Measuring the effect of rotavirus vaccination in primary and secondary care in Merseyside, UK

Thesis submitted in accordance with the requirements of the University of Liverpool for the degree of Doctor in Philosophy by

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Declaration

This thesis is the result of work performed whilst registered as a candidate for the degree of Doctor of Philosophy at the University of Liverpool. I declare that no portion of the work referred to in this thesis has been submitted in support of an application for another degree or qualification of this or any other university or institute of learning. I, Daniel Hungerford confirm that the work included in this thesis is my own. Where information has been derived from other sources, this has been referenced appropriately.

The overall study design (Chapter 4) was that of myself, Professor Miren Iturriza-Gómara and my supervisors, Professor Neil French, Professor Nigel Cunliffe, Dr Roberto Vivancos and Dr Jonathan Read. I conducted the background literature review on rotavirus and rotavirus infections. The below paragraphs outline contributions to each of studies that constitute the thesis results chapters:

Chapter 3: D. Hungerford conceived of the study, performed the searches, led data extraction and data analysis and produced the manuscript. N. French conceived of the study and contributed to the design, analyses and the interpretation. K. Smith and A. Tucker performed data extraction, contributed to analyses and interpretation. M. Iturriza-Gómara conceived of the study and contributed to the interpretation. C. McLeonard performed the searches and assisted with data extraction. NA. Cunliffe and R. Vivancos conceived of the study and contributed to the interpretation. All authors contributed to the drafted manuscript. All authors read, contributed and approved the final manuscript.

Chapter 5: N. French, NA. Cunliffe, R. Vivancos, M. Iturriza-Gómara, and D Hungerford conceived of and designed the study. D. Hungerford, R. Cooke, DA. Allen and NA. Cunliffe acquired the data; D. Hungerford analysed the data, with advice from JM. Read; all authors interpreted the data; D. Hungerford wrote the manuscript; and all authors reviewed the draft and final manuscript.

Chapter 6: N. French, NA. Cunliffe, R. Vivancos, M. Iturriza-Gómara, and D Hungerford conceived of and designed the study. D. Hungerford acquired the data; D. Hungerford analysed the data, with advice from JM. Read, R. Vivancos and N. French; all authors interpreted the data; D. Hungerford wrote the manuscript; and all authors reviewed the draft and final manuscript.

Chapter 7: N. French, NA. Cunliffe, R. Vivancos, LJ. Bonnett, M. Iturriza-Gómara, and D Hungerford conceived of and designed the study. D. Hungerford acquired the data; D. Hungerford analysed the data, with advice from JM. Read, R. Vivancos, N. Bar-Zeev, LJ. Bonnett and N. French; all authors interpreted the data; D. Hungerford wrote the manuscript; and all authors reviewed the draft and final manuscript.

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List of abbreviations

AGE	Acute gastroenteritis
CA	Community-acquired
CDC	Centers for Disease Control and Prevention
CHIS	Child Health Information System
CCG	Clinical Commissioning Group
CI	Confidence interval
DH	Department of Health (UK)
ED	Emergency department
ELISA	Enzyme-linked immunosorbent assay
FCE	Finished consultant episodes
GI	Gastrointestinal
GP	General practice, primary healthcare giver in the UK.
GLM	Generalised linear model
HA	Healthcare-associated
HR	Hazard ratio
HES	Hospital Episode Statistics
IRR	Incident rate ratio
IMD	Index of Multiple Deprivation
ICD-10	International Classification of Disease version 10
KIT	Knowledge and Intelligence Team with PHE
LSOA	Lower Super Output Area
NHS	National Health Service (England)
NOS	Newcastle Ottawa Scale
OR	Odds ratio
ONS	Office for National Statistics
PCR	Polymerase chain reaction
PHE	Public Health England
RR	Relative Risk / Risk Ratio
rt-PCR	Reverse transcriptase PCR

RNA	Ribonucleic acid
RV1	Rotarix®
RV5	RotaTeq®
RVGE	Rotavirus gastroenteritis
SD	Standard deviation
SE	Standard error
NICE	the National Institute for Health & Care Excellence
UK	United Kingdom
US	United States
USA	United States of America
VE	Vaccine effectiveness
VGE	Viral gastroenteritis
WIC	Walk-in-centre, a community acute health provider
WHO	World Health Organisation

Supporting papers

Publications in Appendix A:

1. Hungerford D, Smith K, Tucker A, et al. Population effectiveness of the pentavalent and monovalent rotavirus vaccines: a systematic review and meta-analysis of observational studies. BMC Infect Dis. 2017 Aug 15;17(1):569. https://doi.org/10.1186/s12879-017-2613-4
2. Hungerford D, Read JM, Cooke RPD, Vivancos R, Iturriza-Gómara M, Allen DJ, et al. Early impact of rotavirus vaccination in a large paediatric hospital in the UK. J Hosp Infect. 2016 Jun;93(2):117–20. https://doi.org/10.1016/j.jhin.2015.12.010
3. Hungerford D, Vivancos R, French N, Iturriza-Gómara M, Cunliffe NA. Ecological assessment of the direct and indirect effects of routine rotavirus vaccination in Merseyside, UK using data from multiple health systems: a study protocol. BMJ Open. 2014 Nov 1;4(11):e006161. http://dx.doi.org/10.1136/bmjopen-2014-006161
4. Hungerford D, Vivancos R, Read JM, Iturriza-Gómara M, French N, Cunliffe NA. Rotavirus vaccine impact and socioeconomic deprivation: an interrupted time-series analysis of gastrointestinal disease outcomes across primary and secondary care in the UK. BMC Med. 2018 Jan 29;16(1):10.

Conference presentations

1. Hungerford D, French N, Cunliffe NA (2017, November). Health inequalities, immunisations and public engagement in Merseyside. Oral presentation at Centre for Global Vaccine Research Meeting 2017, Liverpool, UK.
2. Hungerford D and French N (2017, June). Measuring direct and indirect rotavirus vaccine effectiveness using a novel method for routine health data: A GP birth cohort study, UK. Oral and poster presentation at the European Rotavirus Biology Meeting 2017, Cork, Republic of Ireland.
3. Hungerford D, Vivancos R, Read JM, et al. (2017, March). Impact of national rotavirus vaccination on the burden of gastrointestinal infections across a large metropolitan area, United Kingdom. Poster presentation at the European Expert Meeting on Rotavirus Vaccination (EEROVAC) 2017, Utrecht, The Netherlands.
4. Hungerford D, Read JM, Cook, et al. (2015, November). Early impact of rotavirus vaccination in a large paediatric hospital in the UK. Poster presentation at Institute of Infection and Global Health Day, University of Liverpool, Liverpool, UK.
5. Hungerford D, Cunliffe NA. (2015, May). Advances in the Management of Rotavirus in Children. Global burden of rotavirus gastroenteritis and prevention through vaccination. Invited speaker at Primary Care and Public Health, Birmingham, UK.

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Abstract

Prior to the licensing and introduction of rotavirus vaccines in 2006, rotavirus was the most common cause of severe acute gastroenteritis (AGE) in children <5 years of age, with the majority of disease burden occurring in children under two years of age. In the UK rotavirus was estimated to result in 80,000 general practice (GP) consultations in children <5 years of age each year, together with 45% of hospitalisations and 20% of emergency department (ED) attendances for AGE.

The UK introduced rotavirus vaccination into the routine childhood immunisation programme in July 2013. Whilst rotavirus vaccine impact on severe disease has been well described, uncovering vaccine impact on gastrointestinal (GI) disease outcomes across primary and secondary care is of public health importance; particularly understanding the extent of indirect effect or 'herd' protection. It is also important to ensure vaccine uptake and impact is equitable. As incidence of AGE is highest in the most socioeconomically deprived populations and vaccine uptake is often lower, measuring vaccine impact in relation to socioeconomic deprivation is critical. These themes were addressed through a series of inter-linked studies, for three years post-vaccine introduction (July 2013 to June 2016), in Merseyside, UK.

In Merseyside, uptake of first-dose of rotavirus vaccine was 91.4%, and 86.7% for completion of the two dose schedule. Whilst, the risk of non-vaccination was higher in the most socioeconomically deprived populations.

At a large acute paediatric hospital, after two seasons post-rotavirus vaccine introduction, laboratory confirmed rotavirus gastroenteritis (RVGE) hospitalisations reduced by 84% in vaccine-eligible children <2 years of age and 69% in vaccine

ineligible children 2-4 years of age. Reductions in both hospital- and community-acquired RVGE was comparable (83%).

Interrupted time-series analysis of multiple routine healthcare datasets for three seasons post-vaccine introduction showed that among children <5 years of age, the incidence of RVGE and AGE hospitalisations decreased by 80% and 44%, respectively, ED attendances fell by 23%, walk-in-centre attendances by 32% and GP consultations by 13%. Vaccine impact was greatest during the rotavirus-season and for vaccine eligible age groups. The rate of hospitalisations averted was higher among infants in the most deprived communities compared to the least deprived. In adults aged 65 years or older, AGE hospitalisations fell by 25%.

Analysis of a GP birth cohort of children born between May 2010 and June 2016, demonstrated an overall rotavirus vaccine effectiveness (VE) of 11% against AGE. However, when using established methods to estimate direct and indirect VE, estimates were improbable, suggesting unmeasured confounding, and flawed comparator populations. A novel method using propensity score analysis was developed to deal with these issues through balancing comparator populations. Applying the alternative method produced epidemiologically and biologically plausible direct (8-11%) and indirect (1-4%) estimates of VE against GP consultations for AGE.

In summary, rotavirus vaccination reduced healthcare use for multiple GI disease outcomes across the healthcare system. Effects were greatest in infants, for specific rotavirus outcomes, for severe disease, and in the rotavirus season. Furthermore the reduction of GI disease in older populations suggests ‘herd’ protection. Prioritising vaccine uptake in the most socioeconomically deprived communities is likely to give

the greatest health benefit in terms of reducing population disease burden. Finally, a novel approach for measuring VE has been developed to mitigate against unmeasured confounding. This methodology will be valuable for studies using routine healthcare data to measure the broader public health impact of vaccines using syndromic non-specific endpoints.

1 Introduction: rotavirus and rotavirus infection

1.1 Rotavirus biology and classification

Rotaviruses were first identified in humans in 1973 by Bishop and colleagues in the duodenal mucosa of children with gastroenteritis (1). These virus particles identified by Bishop were linked to earlier descriptions of viruses identified as causing severe diarrhoea in animals (1–3). They were named rotaviruses due to their wheel like structure and icosahedral shape with rotational symmetries (like an old fashioned football) seen under electron microscopy (4).

Rotavirus is a double-stranded segmented RNA virus, with a non-enveloped capsid. The capsid consists of three layers: the inner core, composed of the viral protein (VP) VP2, which contains the viral genome and VP3 and VP1; the middle capsid formed by VP6; and the outer capsid containing VP7 and VP4, which form the viral spikes. The middle capsid antigen (VP6) defines eight groups of rotavirus (A-H). In humans the majority of rotavirus disease is caused by group A rotaviruses (2,5), which are further classified by the sequence diversity of genes encoding their outer capsid. The VP7 is a glycoprotein that determines G-types and the VP4 is protease sensitive protein that determines P types, both of these proteins elicit type-specific neutralising antibody responses (2,5). Furthermore, whole genome sequencing has allowed rotavirus strains to be classified according to genotype constellations based on all 11 genome segments (6,7). For this whole genome classification, the genetic backbone constellation (defined by nine gene segments excluding VP7 and VP4) can be used to define genotype constellations (6,7). Among human group A rotaviruses there are two common genotype constellations: Wa-like and DS-1 like (6,7).

The segmented structure of the rotavirus genome means it is possible for rotaviruses to reassort during infections with multiple strains, and because VP7 and VP4 can segregate independently different G- and P- type combinations can co-circulate (8,9). This exchange of genetic material can lead to emerging novel strains, including zoonotic strains from reassortment between animal and human rotavirus strains (10).

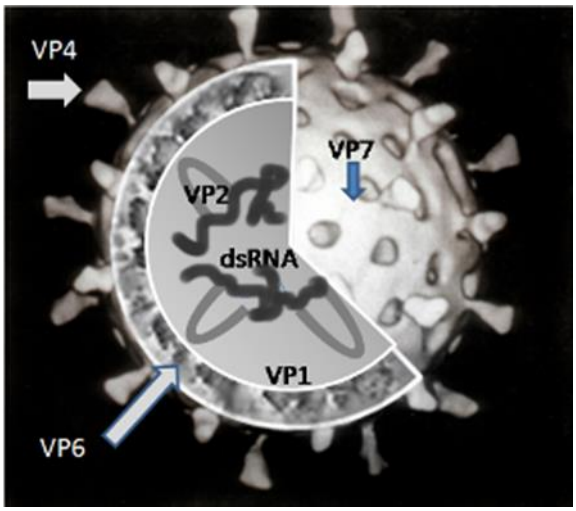

Figure 1-1 Simplified diagram of the location of the rotavirus structural proteins and overall virus structure [Source Graham Colm English Wikipedia]

1.2 Transmission and symptoms

Transmission of rotavirus is by the faecal-oral route and can be person to person, via contact with contaminated surfaces, water and food. Because rotavirus is robust and has a low infectious dose (10-100 virus particles) it is highly transmissible (11,12). Rotavirus infection has a short incubation period, typically between 24 and 48 hours (13), followed by a rapid onset of symptoms of diarrhoea, vomiting and dehydration. Although acute gastroenteritis (AGE) is the most common set of symptoms associated with rotavirus, afebrile and febrile benign convulsions and other neurological conditions have been described (14). The severity of symptoms is variable and depends on a wide variety of host pathogen factors. If symptoms go

untreated infection can result in death, with young children living in low income countries at highest risk.

1.3 Diagnosis of rotavirus infection

There are a number of ways to diagnose rotavirus infection; symptoms alone cannot be used because of shared commonality with other pathogens and non-communicable diseases. However, rotaviruses can be easily detected using standard laboratory procedures, with varying degrees of specificity and sensitivity. Faecal specimens are normally used and because of the high viral load during symptomatic infection, visualisation of viral particles is possible using electron microscopy (2). However, laboratory detection of rotavirus gastroenteritis (RVGE) in humans using electron microscopy has low sensitivity. This technique was replaced with antigen based assays, such as enzyme-linked immunosorbent assay (ELISA) using antibodies against the inner capsid antigen VP6 (15). This method is recommended by the World Health Organization (WHO) and correlates well with clinical disease but commercial ELISA kits generally can only detect group A rotaviruses (16). Diagnostic testing protocols for rotavirus differ between countries / regions and must therefore be considered when describing disease (17,18).

Molecular techniques such as, reverse transcription-quantitative polymerase chain reaction (qRT-PCR) can be used to detect rotavirus in stool samples and distinguish between rotavirus groups. Furthermore qRT-PCR can be used to identify G and P types using standardised methodologies (17,18). The sensitivity of qRT-PCR compared to ELISA means that it can detect rotavirus shedding in faecal samples from asymptomatic individuals (16,19,20). Due to the good correlation between ELISA and clinical disease it has been used to identify cut-offs for qRT-PCR

equivalent to clinical disease (21,22). These cut-offs have become more important as molecular techniques are used more frequently in diagnostic laboratories.

1.4 Rotavirus epidemiology

1.4.1 Infections and susceptibility

During a person's life they experience repeat rotavirus infections often as asymptomatic episodes. Rotavirus has normally infected the majority of children by 3-5 years of age (5). Severe symptomatic infection normally follows primary or early exposure to rotavirus, a level of protection is then provided against subsequent infections (23). A prospective birth cohort study from Mexico showed that 96% of children under 2 years had experienced a primary rotavirus infection. Also, showing that following primary infection the host / child has reduced susceptibility to secondary infections and that subsequent infections are more likely to be caused by different genotypes to that causing primary infection (24). The nature of host susceptibility helps to drive the age distribution of symptomatic cases with the majority occurring in children 4-24 months of age (2,5,25). Older children having already had multiple infections and therefore reduced susceptibility. Thus, by late childhood and adulthood, severity and frequency of clinical disease has declined; with the proportion of asymptomatic infections relative to symptomatic infections increasing (5,24). However, epidemiology of rotavirus infections in older children and adults is heavily affected by case presentation to healthcare establishments and testing protocols (26).

1.4.2 Global rotavirus disease burden in children under 5 years

Prior to licensing and routine use of rotavirus vaccination, rotavirus was the leading cause of AGE in children under the age of five years. Rotavirus was estimated to be responsible for 450,000 deaths globally (Figure 1-2); with over 90% of deaths

occurring in developing countries (27,28). Whilst mortality from rotavirus infections is low in high income countries they do cause substantial severe morbidity and burden on healthcare resources (29,30). Using a range of country specific incident rates from 1986-2000 it was estimated that in high income countries that rotavirus causes 223,000 (range 142,000–358,000) hospitalisations and 7,122,000 (range 2,123,000–17,881,000) episodes of RVGE requiring only home care per year (28). Rotavirus is also an important cause of nosocomial (healthcare-acquired) diarrhoea in children under 5 years of age. In Europe rotavirus was estimated to be responsible for 31-87% of paediatric nosocomial diarrhoea (31).

In the USA rotavirus has been estimated to cost over $300 million to the healthcare system and nearly $1 billion in society costs (e.g. loss of earnings, childcare) (32).

Figure 1-2 Estimated rotavirus disease burden in children <5 years of age, prior to rotavirus vaccine introduction (28)

1.4.3 Seasonality

Seasonality of rotavirus infections is very variable by geographical region. There has been speculation that genotype diversity, geographical location, climate and country development level all affect seasonality. However, there is no evidence that there is one unifying factor that explains why some regions have seasons and others experience year round disease (33). In Western Europe there is strong seasonality of disease in the Northern Hemisphere during the winter / spring months (Figure 1-3). There is some indication that rotavirus infections spread in Europe from South to North and West to East, with similar patterns described in the US (18,34–36). A recent review of global studies established that high income countries experience disease patterns which were more likely to be seasonal (33).

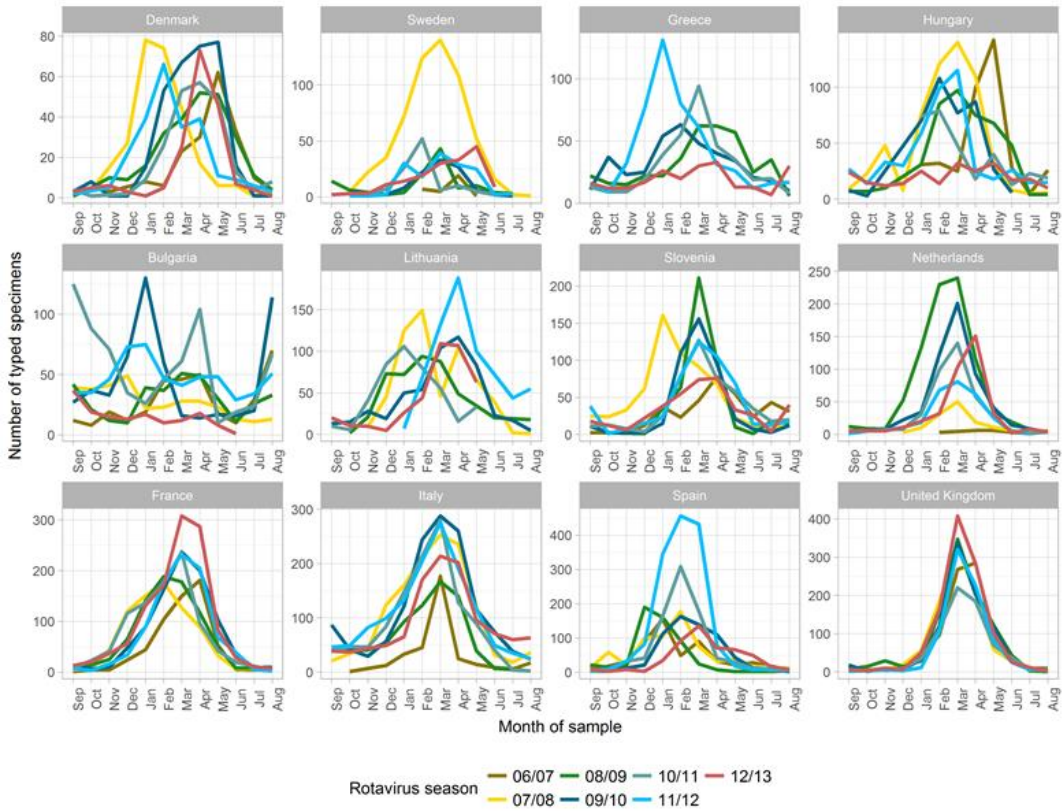

Figure 1-3 Rotavirus seasonality in European countries participating in EuroRotaNet rotavirus surveillance network; prior to routine rotavirus vaccine introduction, September 2006 to August 2013 [EuroRotaNet data (17)]

1.4.4 Epidemiology in adults

While the epidemiology and disease burden of RVGE in infants and young children is well described, the burden of rotavirus disease in older children and adults is less well understood. Whilst nearly all adults would have been infected by rotavirus across their life, rotavirus infections in adults are normally milder than in young children resulting in less clinical presentation (37–39). Furthermore the rates of infection and clinical presentation with symptoms is variable by geographical area and a country's level of development (40). In the early 1980s a small hospital based study in the UK investigated the aetiology of acute diarrhoea hospitalisations in 73 adults and identified that 4% were caused by rotavirus (41). Similarly rotavirus was identified in 3% of adults with diarrhoea presenting at a Swedish infectious disease clinic (42), and 5% of adults admitted to hospital with diarrhoea in Thailand (43). A hospital based surveillance study in Bangladesh also identified rotavirus in 4% of ≥60 year olds with diarrhoeal disease (44). There have however, been studies in adults in which rotavirus is detected more frequently. Another small study conducted in Australia in 74 adults with acute diarrhoea identified rotavirus as the second most common pathogen (17%) and a Mexican study identified rotavirus in 64% of adults with moderate to severe AGE (45,46).

Whilst most studies have been in the hospital setting focusing on moderate to severe RVGE, there is limited research on RVGE in adults in the community setting. A prospective surveillance study conducted in the UK showed that in those aged 5 years and older, rotavirus was detected in approximately 4% of primary care consultations and 3% of community episodes for infectious intestinal disease (30,47).

Several studies have also indicated that whilst endemic rotavirus season is driven by young children, adult disease is less season-specific, instead, occurring all year

(36,40). Although, rotavirus infection does occur in adult settings, such as long-term care facilities (48), the highest risk of rotavirus infection in adults appears to be in adults in contact with children with rotavirus infection (37–39). These findings suggest exposure to rotavirus is likely to vary dramatically over a person's life and that young adults without dependents would be at the lowest risk of exposure to rotavirus.

1.5 Prevention of rotavirus gastroenteritis

Rotavirus can spread easily and infects nearly all children in early life, although good cleanliness and hand washing are good practice, routine handwashing in the home is ineffective at reducing rotavirus transmission (49–51). Whilst programmes which improve sanitation, hygiene and water supply in low-income countries is estimated to reduce diarrhoeal disease incidence by approximately 30%, the comparable rates of rotavirus disease (not severity) in low- and high-income countries (despite better sanitation in high-income countries), indicate that these improvements have minimal impact on rotavirus transmission (50,52–54). Therefore, vaccination against rotavirus currently represents the most effective preventative measure against rotavirus disease (49,51,54).

1.5.1 A brief history of rotavirus vaccines

Research into the development of vaccines against RVGE began in the late 1970's. Using animal models it was demonstrated that previous infections with animal strains protected an animal from infection with human rotaviruses (55). Therefore it was supposed that live attenuated (reduced virulence) animal strains when given to humans orally could copy the immunity conferred by natural infection and prevent severe disease (14,54). This led to the development of live attenuated animal reassortment vaccines; however, field trials indicated variable efficacy (56–58).

Because of the broad diversity of rotaviruses any vaccine needs to show good cross-protection against the predominant genotypes. Therefore, to achieve better cross-protection, multivalent human - animal reassortment vaccines and live attenuated human rotavirus vaccines have been developed (5).

The first licensed rotavirus vaccine was RotaShield® (Wyeth Laboratories) and it began use in the US in 1998. However, RotaShield® was withdrawn from use in 1999 following associated incidences of intussusception (59). Intussusception is when one segment of the intestine folds into another section of the intestine and can result in an obstruction, whilst intussusception can occur in non-vaccinated infants and can be remedied using medical procedures, it is potentially fatal (60).

Although RotaShield® remained licenced it was removed from use. Subsequently, since 2006, two major vaccines have been licensed for use; a three dose pentavalent human-bovine reassortment vaccine (RV5, RotaTeq®, Merck & Co., Inc.) and two dose live attenuated monovalent vaccine (RV1, Rotarix®, GlaxoSmithKline Biologicals, Belgium) (54) (Table 1-1).

Clinical trials have shown both to be highly effective. In high-income countries with low mortality rates the vaccine efficacy in the first two years of follow-up is over 80% against severe (defined using a score cut-off from either a Clark or Vesikari Clinical Severity Scoring System) rotavirus disease (61–63). But as income declines and mortality increases the efficacy of the vaccines decrease, with reported efficacy of ~39-49% in countries with high mortality rates (61,64,65). Although the efficacy is lower in high mortality countries the absolute benefit is substantial due to the higher baseline burden of disease (66). Currently no one factor has been identified as being responsible for the lower efficacy of the vaccines in high mortality countries.

There has been speculation that this is due to lower systemic immune response to both natural infection and rotavirus vaccination (67). Indeed two recent nested-case control studies of Ghanaian and Pakistani infants has suggested that the composition of the gut microbiome correlates with the immunogenicity of rotavirus vaccines and could be contributing to the reduced efficacy in developing countries (68,69).

A further consideration is whether these rotavirus vaccines can induce heterotypic immunity. This is crucial, because of the variety of rotavirus strains circulating co-currently, which may be heterotypic to the G and P types contained in the vaccine. Efficacy studies have indicated that both RotaTeq® and Rotarix® provide heterotypic protection, although this may be to a reduced degree for strains with G or P types which do not match the vaccine strain (54,70,71). Reassuringly a recent meta-analysis of the strain specific effectiveness of rotavirus vaccines also suggest that both vaccines exert similar protection against homotypic and heterotypic rotavirus strains (72). However, an important component of the long-term evaluation of rotavirus vaccine programmes will be the continued surveillance of rotavirus strain distributions to identify possible vaccine induced changes in rotavirus strain distributions and any emerging new strains.

As of April 2017 over 90 countries had introduced rotavirus vaccination into national immunisation programmes worldwide and many more have rotavirus vaccine available at state level or via private healthcare insurance (Figure 1-4) (73). Since the first introduction of the current era of rotavirus vaccines in 2006, observational and ecological studies have been conducted to assess the effect of rotavirus vaccines in the ‘real world’. The next section provides an overview of methodologies that are being employed to assess the effect of rotavirus vaccines after introduction into public health programmes.

Table 1-1 Details of two licensed rotavirus vaccines.(16)

	Rotarix® GlaxoSmithKline Biologicals	***RotaTeq***® Merck & Co
Indication	For the active immunisation of infants aged ≥6 weeks against RVGE	
Composition	Live attenuated monovalent human rotavirus strain G1P[8]	Live attenuated pentavalent bovine (WC3)-human reassortant strains G1P[5]; G2P[5]; G3P[5]; G4P[5]; G6P[8]
Form	Orally administered in liquid formulation	
Administration	• Two doses • First dose from 6 weeks of age • Minimum of 4 weeks between doses • Schedule should be completed by 24 weeks of age	• Three doses • First dose between 6 and 12 weeks of age • Minimum of 4 weeks between doses • Schedule should be completed by 26 weeks of age

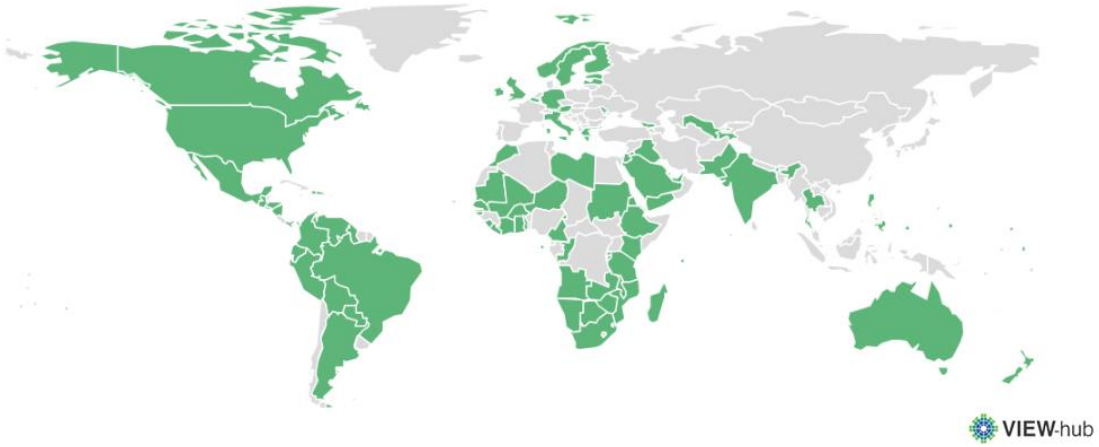

Figure 1-4 Countries that have introduced rotavirus vaccine

[Source: IVAC, accessed 20th February 2018]

1.6 Methodologies for measuring population vaccine effectiveness and impact

Vaccines can have an effect at both the individual (direct protection) and population level (indirect protection) (74). Vaccine efficacy represents the direct effect of vaccination in individuals receiving vaccine under rigorously controlled conditions (75). This is normally measured in pre-licensure clinical trials. Whereas, vaccine effectiveness (VE) is for measuring vaccine performance in a population after vaccine introduction (76–78). Observational studies are the principal study design used for calculating VE (79). These studies are informative to public health as they measure both the effect on the individual and the population (74,77). The types of population effect include the indirect, total and overall effect. The indirect effect is the herd protection conferred by the vaccine on the unvaccinated (76); the total effect is a combination of the direct effect and indirect on vaccinated individuals (77,79); and the overall effect is a population weighted combination of the indirect effect on unvaccinated individuals and the total effect in vaccinated individuals. This overall effect allows health authorities to evaluate the population impact of a vaccine programme including calculation of vaccine cost-effectiveness (80,81).

To measure the direct effect studies normally require one population in which the vaccine is available and then a comparison of the measured outcome in those that have received the vaccine with those that have not (77,79,80). In order to measure the indirect, total and overall effects of vaccination two populations are required, one with and one without vaccination. These populations are normally separate in time and / or space (Figure 1-5) (77). The epidemiological study designs employed for measuring VE predominately include: case-control, cohort, screening, outbreak, and ecological. Each design has biases and pros and cons, and the type of effect which

can be measured principally depends on the study design and the populations being compared (Table 1-2) (77). There are also serological studies, such as correlates of protection, which focus on a measurable biological response such as antibody titres (82–84). If this response is correlated to disease then they can be used for vaccine evaluations. The sections below describe the most common epidemiological study designs for assessing VE and population impact.

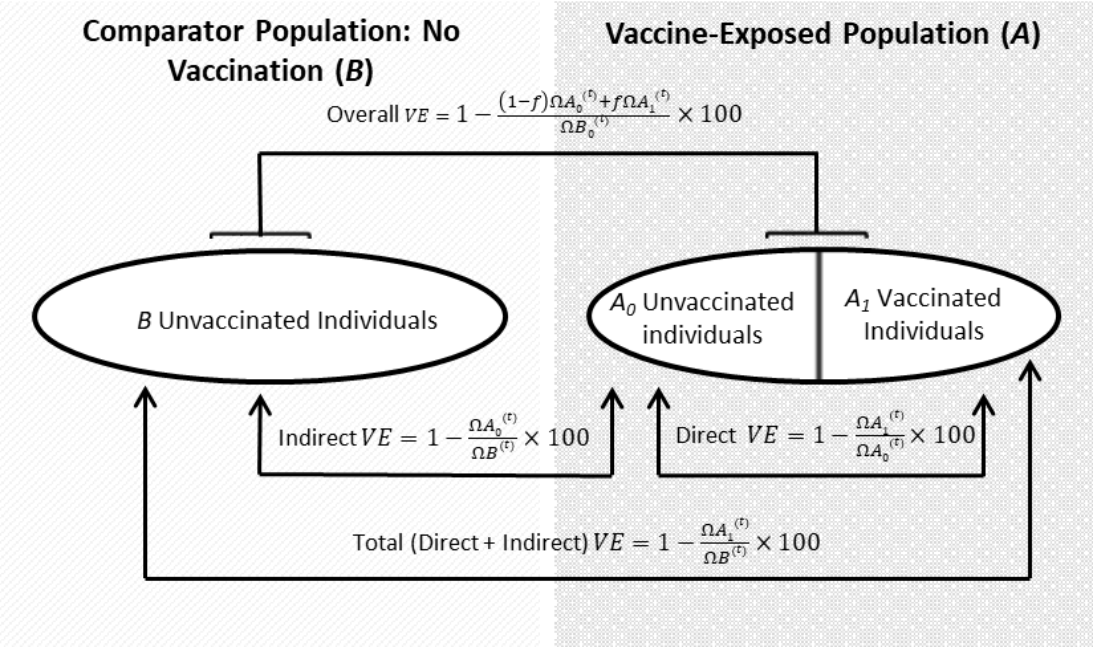

Figure 1-5 Types of vaccine effect and comparison populations [VE is the Vaccine effectiveness, where Ω is the attack rate (the proportion of cases in a defined population); f is proportion of the population vaccinated; t is time.] (74,77,85)

Table 1-2 Study design and effect type

Study type	Effect type			
	Direct	Indirect	Total	Overall
Cohort	Yes	Yes	Yes	Yes
Outbreak	Yes	No	No	No
Case-control	Yes	No	No	No
Screening	No	No	No	Yes
Ecological	No	No	No	Yes

Cohort studies

These are normally conducted by comparing the incidence of an outcome / disease in a cohort of vaccinated and unvaccinated persons over a period of observation, either prospectively or retrospectively (83,84). Prospective studies are utilised less frequently to measure VE due to cost, time and subject dropout (82). However, they have been used to measure the long-term effectiveness of varicella vaccination in children, influenza VE in older adults and to assess VE of catch-up vaccine campaigns during disease outbreaks (86–88). A prospective cohort study can be affected by a number of potential biases. Some of these biases fall under a broad grouping of selection bias; error introduced when the population under study do not accurately represent the general or target population, resulting in reduced external validity (89,90). Types of selection bias include: loss to follow-up bias (attrition bias), when those who drop out of the study differ systematically from those that are not lost; non-response bias, when those who enrol in the study are different from those who did not. The healthy entry / healthy worker bias is an example of non-response bias, when the study includes individuals at baseline that would be likely to be more healthy than the general population (90–92).

Other biases that are commonly present in cohort studies are information bias and confounding. Response bias is a type of information bias, which could occur if participants systematically under report behaviour or health issues that may affect the chance of outcome, an example of this may be underreporting alcohol use (90). Confounding can occur when a variable has an association with both exposure (vaccination) and outcome (disease). For example, healthcare seeking behaviour / healthcare access can be an important confounder in some observational studies.

Confounding, information bias and selection bias need to be appropriately controlled for in study design or in the study analyses (89,91).

In retrospective cohort studies that involve primary data collection the chance of bias is increased compared to a prospective study, through recall bias (83).

A version of the cohort study commonly used to measure VE is those using pre-established healthcare databases which include information on exposure (vaccination) and outcome (disease) (85,93–95). It is important in these studies that chance of exposure to the outcome is equal between groups or that adequate statistical approaches are applied to mitigate for any inequality (96). Often differences in health-seeking behaviour between vaccinated or unvaccinated individuals can lead to under ascertainment of the outcome and bias in VE estimates (82,97). Unlike case-control studies cohort studies avoid bias associated with selecting inappropriate controls and also often allow the calculation of all four effect types (82,85), although the accuracy of these estimates can be variable depending on the occurrence of cofounders in comparator populations (85). In cohort studies typically there is a time element so that survival, relative incidence rates or relative hazards can be calculated for vaccinated versus unvaccinated groups. Therefore cohort studies will normally measure VE through the formula: $\mathrm{E} = (1 - \mathrm{RR}) \times 100$, where RR is the relative risk; or, $\mathrm{VE} = (1 - \mathrm{HR}) \times 100$, where HR is the hazard ratio.

Case-control studies

Case-control studies are the most common study used in ‘real world’ VE studies (80,83,84,98). However, only the direct effect of a vaccine programme can be calculated in this design. They recruit based on the endpoint (cases of disease) and

establish a control comparator of individuals who have not experienced the outcome of interest (79,83,84). It is important that the end-point is specific because non-specific endpoints can change over time and setting (99). Vaccine status is established retrospectively for both groups, normally along with baseline characteristics and confounders that may be adjusted for in analyses. These methods can be relatively cheap and rapid, but can be problematic if a vaccine programme is: highly effective with a large herd effect resulting in a lack of cases; and / or vaccine uptake is so low or high that unvaccinated population are likely to have a different disease risk to the general population independent of vaccination; and / or vaccine uptake is so high most cases are vaccinated so that a larger sample size is needed to detect a significant difference in vaccination status between cases and controls. Therefore, to increase power and reduce sample size, case-control studies are best implemented when vaccine coverage is between 20-80% (100).This may be easiest to achieve if the study is conducted as soon as possible after the start date of the vaccine programme (99).

It is also important that cases and controls have an equal risk of exposure and that vaccine status is collected in the same robust way from both cases and controls (83,97). Often a matched case-control design is utilised using factors such as age, sex and geography (99). This is usually for convenience, improving efficiency and /or precision or for control in the analysis of unquantifiable social, environment or biological factors (101). However, it is a common misconception that matching reduces confounding and it may actually increase the chance of confounding if the factors matched are not present in the overall population (101).

The use of test negative-controls is common in case-control studies. Test negative-controls are controls, which have the same symptoms as the cases but were negative

for the pathogen of interest. It is often logistically advantageous, cost-effective and provides a high-degree of comparability between controls and cases because both controls and cases are from the same single source (99). It can help to minimise selection bias because cases and controls are assumed to have similar health-seeking behaviour reducing outcome ascertainment bias (97). A limitation of the test-negative design is that there is an assumption that the vaccine under study has no effect on disease incidence in the controls. In case-control studies VE is predominately measured using a rate difference with the Odds Ratio (OR) in the formula: $VE = (1 - OR) \times 100$.

Screening studies

The screening method is a variation on the case-control and cohort methodologies, in this design the entire population or a sample of the population is used as a reference (102–105). In screening studies the number of cases with the outcome of interest is required as is the number of cases vaccinated; the comparator is then the vaccine uptake in the reference population (84,102). This is less resource intensive than retrospective case-control studies and primary data collection cohort studies. Whilst the screening method has a role to play in measuring VE it is limited. The method is designed to be a rapid preliminary assessment of VE when attack rate data is unavailable. As the screening method uses secondary data analysis it is subject to the associated biases and relies on accurate measurement of vaccine coverage.

Furthermore, when herd immunity is provided by a vaccine, and population incidence declines in the unvaccinated, the screening method will underestimate VE (102). Therefore, the appropriateness of using the screening method is dependent on the target vaccine, data quality, and the population; and may need to be followed up

with more robust observation methodologies. To measure VE using the screening study design the following formula is therefore used: $VE = (\frac{PCV}{1-PCV}) \times (\frac{1-PPV}{PPV}) \times 100$, where PCV is the proportion of cases vaccinated and PPV is the proportion of the total reference population vaccinated.

Outbreak studies

These studies are best conducted after a disease outbreak in a defined population setting such as a school, establishment or city (106–108). In outbreak studies measurement of VE is during a defined time-period and setting, using data on whether people became infected and / or developed disease in a defined population. Relative risk based on cumulative incidence or relative attack rates (the number of cases in a specific population dived by population under study) will be used to calculate VE: $\mathrm{VE} = (1 - \mathrm{RR}) \times 100$, where RR is the relative risk.

Ecological – population vaccine impact

These studies normally measure a disease over time e.g. “before and after” vaccine introduction. In these types of studies good quality surveillance data is required for a number of year’s pre and post-vaccine introduction, any temporal or seasonal trend must be taken in to account when assessing a change in disease burden. Temporal ecological studies remove the concerns of confounding through health status and health seeking behaviour associated with exposure (vaccination) because they do not compare the disease incidence in the vaccinated with that in the unvaccinated (97). However, in these studies there is the issue that any change or no change in disease incidence could be a result of the vaccine or some other factor, natural or otherwise (e.g. change in healthcare provision, data quality). Also, within this design there is the possibility of reducing some of this cofounding if the vaccine programme has

been introduced in phases, group by group (83). In this case a stepped wedge design can be utilised; groups of vaccinated and those yet to be vaccinated are compared, this could involve random or programmatic selection of groups (84,109). Confounding would be reduced as the groups under comparison should have similar base-line characteristics (83).

A common study design for measuring population vaccine impact in the 'real world' is the interrupted time-series (ITS) (110–113). In the context of vaccine evaluations the ITS methodology would follow a disease outcome, over time, prior to an intervention (vaccination) to establish a baseline trend and seasonality, then under a hypothetical situation where vaccine introduction did not take place the counterfactual trend is predicted for the post-vaccine period and compared to the actual post-vaccine trend (110). A percentage change can then be calculated from this comparison. There is further complexity to the ITS design depending on how the vaccine is introduced, for instance, vaccine uptake that reaches a steady state almost instantly as a one off step / level change or gradual introduction could be analysed as multiple steps (111).

In reality many published studies which assess vaccine impact are limited in the robustness of the analyses by the available data. Often a more crude "before and after" approach is used; in which mean / median incidence from the pre-vaccine period is compared to the post-vaccine introduction years, with little or no adjustment for trend or seasonality (114). Nevertheless, ecological study designs using both ITS and simple "before and after" methods have been used to evaluate the population impact of a number of vaccines including pneumococcal conjugate (115–119), varicella (120), influenza (121,122), and rotavirus (112–114,123).

In summary, whilst there are variations on all these study designs, such as the case-cohort, cohort and case-control studies contribute the majority of VE studies assessing individual level vaccine effects. Whereas studies aiming to assess vaccine impact at the population level will usually utilise an ecological design with varying degrees of rigour.

1.7 Impact of rotavirus vaccination in high income countries

Since licensing of Rotarix® and RotaTeq® in 2006, the global mortality from rotavirus diarrhoea in children <5 years of age has decreased substantially; from an estimated 528,000 in 2000 to 215,000 in 2013 (124). While the majority of this reduction has resulted from vaccine introduction in low-middle income countries (124), many high-income countries have also introduced rotavirus vaccination. Belgium and the USA introduced rotavirus vaccination in 2006, followed by Austria and Australia in 2007, Finland in 2009 and Israel in 2010. There are also a number of countries that have introduced the vaccine privately or regionally, such as in Germany, Greece, Italy, and Spain. More recently countries such as, Germany, Ireland and Norway, have introduced country wide vaccination. Chapter 3 in this thesis provides a systematic review and meta-analyses of observational case-control and cohort studies measuring rotavirus VE, whereas studies assessing the overall public health impact of rotavirus vaccination through ecological study design are described below.

The majority of rotavirus impact studies have been retrospective using routine healthcare databases to assess a change in disease burden post-vaccine introduction relative to a pre-vaccine baseline. There have also been a few prospective surveillance studies. A number of rotavirus specific outcome measures have been reported, predominately RVGE hospitalisations, RVGE laboratory detections and

less frequently, RVGE ED visits and RVGE outpatient / GP visits. There have also been reports on less-specific disease outcomes such as AGE hospitalisation, AGE ED visits and AGE outpatient attendances, as well as, diarrhoeal disease outpatient / GP visits. As the US was one of the first countries to introduce rotavirus vaccination the majority of published impact studies have been conducted in the US.

Impact on RVGE and AGE hospitalisations

In the US RotaTeq® was first recommended in 2006 for routine childhood vaccination, this recommendation was expanded to include Rotarix® in 2008. Vaccination coverage is variable by state ranging from ~55% to 85% in 2013 for 19-35 month olds (125). Impact studies covering seasons 2008, 2009 and 2010 showed reductions of between 55% and over 80% in RVGE hospitalisations in children <5 years of age and reductions in all-cause AGE hospitalisations of between 29% and 50% (126–133). These included studies of: national and state level health databases; a sub-national active surveillance study from the New Vaccine Surveillance Network of rotavirus diarrhoea; an insurance claims database study; and, local hospital based studies of laboratory confirmed rotavirus (126–133). The largest reductions in these studies were in vaccine eligible infants <12 months of age and 1 year olds, with a number of these studies also showing evidence of herd protection among unvaccinated groups (132,133). Additionally, data from the national healthcare database, from hospitals in 42 states, showed significant reductions in both RVGE coded discharges and all-cause AGE hospitalisations in 2008, 2009 and 2010 among 5-14 year olds and 15-24 years (134,135). These reductions were highest during the winter / spring peak rotavirus season strengthening the evidence for an indirect effect of rotavirus vaccination.

Australia introduced rotavirus vaccination in specific states / territories that had high RVGE disease burden in 2006, followed by full inclusion in the national immunisation programme in 2007. Both Rotarix® and RotaTeq® are used in Australia, dependent on the state / territory choice. National vaccine uptake reached over 80% in 2007 and 2008 (136). In a national healthcare database study RVGE hospitalisations in children under 5 years of age reduced by 67% and 45% in 2007/08 and 2008/09, respectively (136). There was also a 38% decline in non-rotavirus coded AGE hospitalisations in 2009/10 (137). A one site paediatric hospital study of RVGE hospitalisations in children aged under 5 years of age showed similar reductions of over 65% in 2008-2009 (138). Herd protection from rotavirus vaccination was also suggested through a further study at the same hospital site with reductions in RVGE hospitalisations in older age groups, including those ineligible for vaccination (139).

Belgium introduced vaccination in 2006 and achieved over 90% uptake of vaccine (predominately Rotarix®) rapidly (140). There were large reductions in RVGE hospitalisations in the vaccine eligible age group of between 60-80% (141) and smaller but significant reductions in older children (141,142).

Since vaccine introduction in Austria, both RotaTeq® and Rotarix® vaccines have been used at different times, vaccine uptake was reported at over 87% by 2008, and in age eligible children up to 20 months of age RVGE hospitalised cases decreased by 74% in the first full surveillance year post-vaccine introduction (143,144). This impact has been sustained in children under two years of age up to 4 years after introduction, with reductions of over 80% (145). Older vaccine eligible cohorts have also seen sustained reductions of over 60% in children 2-3.5 years (145). Herd protection is also likely; there were small reductions of approximately 20-22% in

unvaccinated older children in 2008 and 2009 (143). However, caution is required, as in 2011, increases in RVGE hospitalisations were seen in children aged 5-14 years (145).

In Finland where RotaTeq® is the sole vaccine in use, vaccine uptake reached over 95% for the full schedule comparable to other childhood vaccines (146). In the first complete season post-vaccine introduction, RVGE hospitalisations fell by 80% in infants and all-cause AGE hospitalisations fell by over 54%. Herd protection was also indicated with RVGE hospitalisations falling by over 53% and AGE hospitalisations falling by over 27% in children aged 1-4 years who predominately would have been vaccine ineligible (146). The impact of vaccination in Finland has been shown to be sustained up to 3 years post-vaccine introduction (147,148).

In Germany routine rotavirus vaccination has been recommended by regional health authorities since 2008. Rotavirus vaccine was only available through health insurance in some states, and state-based coverage ranged from 11% to 77% (140,149). Since 2013 vaccination has been recommended nationally (both RotaTeq® and Rotarix® vaccines are available) and vaccine coverage has increased; although remains variable across states (149). Currently, there are no vaccine impact studies post-national recommendation. However, an early study compared vaccine impact on RVGE hospitalisations in Western States (vaccine uptake ~58%) and Eastern States (vaccine uptake ~ 22%) between 2008 and 2011 (150). In children <2 years of age reductions were 35% in Western States compared to 25% in Eastern States. A further study analysing data from 2006-2012, showed that in areas reaching 64% vaccine uptake there was a 60% reduction in RVGE hospitalisations in infants < 1 year of age compared to 19% in low uptake areas (149). Small reductions were

also seen for all-cause AGE hospitalisations. However, there was no reduction in RVGE hospitalisations in children 2 and 3 years of age detected.

In Israel RotaTeq® was introduced into the national immunisation programme in 2010, with vaccine uptake around 80% (151). In a prospective study in 3 acute hospitals, conducted 2008-2015, the incidence of RVGE hospitalised fell by 61%, and AGE hospitalisations by 34% in children under 5 years of age (151).

In Spain vaccination has not been recommended for inclusion in the childhood immunisation schedule, however vaccination is available privately (only RotaTeq® since 2010) but vaccine coverage is low –moderate (140). National and regional studies have shown a reduction in RVGE hospitalisations and AGE hospitalisations, since vaccine introduction (152,153). However, the most significant finding occurred after a withdrawal of rotavirus vaccination for six months in 2010, due to the detection of DNA fragments of porcine circovirus in both Rotarix® and RotaTeq® (154). Subsequent analysis showed a drop in vaccine coverage and in parallel RVGE hospitalisations in infants increased by 260% in 2010/11 compared to the previous season (2009/10). However, reductions in RVGE hospitalisations resumed when vaccination was re-established (155).

Impact on RVGE and AGE outpatient / primary care visits

The impact of rotavirus vaccination on RVGE and AGE outpatient / primary care visits has been less well described. In Finland hospital outpatient reductions in RVGE were similar to that in inpatient cases for infants <12 months of age (79%) and 1 year olds (73%). There were lower but non-significant reductions in children 2-4 years of age (146). A retrospective health record study in New Orleans, USA showed significant decreases in all-cause AGE primary care visits between 2007 and

2009; 29% for infants <12 months of age and 18% in predominately vaccine ineligible children aged 2-4 years (156). Again in the US, an insurance claims database study estimated similar reductions in all-cause diarrhoea-associated outpatient visits of 21% and 24% among infants <12 months of age for the 2008 and 2009 rotavirus seasons (January to June), respectively (128). Reductions were lower among children 1 year of age. In 2-4 year olds a 8% reduction in 2008 was followed by a 10% increase in 2009 (128).

Impact on hospital-acquired rotavirus

Studies from the US, Australia, Austria, Belgium and Germany have all shown reductions in hospital-acquired RVGE comparable to community-acquired RVGE hospitalisations (131,139,142,150,157). This is indicative of a reduction in rotavirus transmission in the hospital setting. This is an important aspect of rotavirus vaccination as this should help protect hospitalised children with severe disease and comorbidities from exacerbation of underlying illness through hospital-acquired rotavirus infection.

2 Thesis overview

2.1 Project starting points

The stimulus for this project was the introduction of routine rotavirus vaccination into the UK's childhood immunisation schedule in July 2013 (158). Whilst the impact of rotavirus vaccine on severe disease has been well described, uncovering the impact of rotavirus on a "total health economy", across primary and secondary care for rotavirus-specific and non-specific gastrointestinal outcome measures is yet to be documented. Furthermore, since it is known that in the UK the incidence of all-cause acute gastroenteritis is highest in the most socioeconomically deprived populations and vaccine uptake is often lower in these populations (159–163), measuring vaccine impact in relation to socioeconomic deprivation is critical to assess whether vaccine uptake and impact is equitable.

2.2 Aims and objectives

Aim: To use routine healthcare data sources to estimate the direct and indirect impact of rotavirus vaccination on gastroenteritis indicators in the population of Merseyside, UK, in relation to vaccine coverage and sociodemographic indicators.

Study objectives:

The following questions will be addressed:

- Is there a significant change in:
    - Laboratory detections of rotavirus in faecal samples?
    - Admissions to hospital for rotavirus or acute gastroenteritis?
    - Attendances to emergency departments for gastrointestinal conditions?

    - Hospital-acquired cases of rotavirus infection?
    - GP and Walk-in-Centre consultations for gastroenteritis / diarrhoea?
- What is the extent of indirect vaccine effectiveness or herd protection?
- Is there a relationship between socioeconomic deprivation, vaccine uptake and vaccine impact?

2.3 Outline of thesis

The thesis contains a general introduction to rotavirus in chapter 1 and at the end a general discussion (Chapter 8). Chapter 3 includes a peer review published systematic review and meta-analysis of rotavirus vaccine effectiveness studies. The general methods chapter (chapter 4) includes the data sources and methods adapted from the published study protocol. The results chapters 5, 6 and 7 are in the form of studies written for publication and include, detailed methods and discussion:

- The work encompassed in chapter 3 is published in BMC Infectious Diseases
- The protocol presented in chapter 4 is published in BMJ Open
- The study presented in chapter 5 is published in the Journal of Hospital Infection
- The study presented in chapter 6 is published in BMC Medicine
- The study presented in chapter 7 has been submitted for publication

When the work for this thesis began the intention was to measure population vaccine impact in an ecological study design. However, in the process of sourcing data for the analysis of rotavirus vaccine impact on GP consultations, an important opportunity was identified. This prospect was to undertake a methodologically rigorous analysis of rotavirus vaccine effectiveness using a birth cohort design. This analysis would allow the different component of vaccine effectiveness to be

calculated and add important evidence of vaccine effectiveness on less severe / moderate disease burden, which is currently lacking from the literature. Therefore, a National Health Service (NHS) Research Ethics Committee study amendment for the addition of the GP birth cohort study was submitted and favourable opinion received in November 2014 (Appendix B). The GP birth cohort study began in parallel to the impact study and is described in its entirety in results chapter 7.

3 Population effectiveness of the pentavalent and monovalent rotavirus vaccines: a systematic review and meta-analysis of observational studies

3.1 Abstract

Background: Rotavirus was the leading cause of acute gastroenteritis (AGE) in infants and young children prior to the introduction of routine vaccination. Since 2006 there have been two licensed vaccines available; with successful clinical trials leading the World Health Organization to recommend rotavirus vaccination for all children worldwide. In order to inform immunisation policy we have conducted a systematic review and meta-analysis of observational studies to assess population effectiveness against AGE.

Methods: We systematically searched PubMed, Medline, Web of Science, Cinhal and Academic Search Premier, plus grey literature sources for studies published between January 2006 and April 2014. Studies were eligible for inclusion if they were observational measuring population effectiveness of rotavirus vaccination against healthcare attendances for rotavirus gastroenteritis (RVGE) or AGE. To evaluate study quality we use used the Newcastle-Ottawa Scale for non-randomised studies, categorising studies by risk of bias. Publication bias was assessed using funnel plots. If two or more studies reported a measure of vaccine effectiveness (VE), we conducted a random effects meta-analysis. We stratified analyses by World Bank country income level and used study quality in sensitivity analyses.

Results: We identified 30 studies, 19 were from high income countries and 11 from middle-income countries. Vaccine effectiveness against hospitalisation for laboratory confirmed RVGE was highest in high income countries (89% VE; 95%

CI 84-92%) compared to middle-income countries (74% VE; 95% CI 67-80%). Vaccine effectiveness was higher for those receiving the complete vaccine schedule (81% VE; 95% CI 75-86%) compared to partial schedule (62% VE; 95% CI 55-69%). Two studies from high-income countries measured VE against community consultations for AGE with a pooled estimate of 40% (95% CI 13-58%; 2 studies).

Conclusions: We found strong evidence to further support the continued use of rotavirus vaccines. Vaccine effectiveness was similar to that reported in clinical trials for both high and middle-income countries. There is limited data from low-income settings at present. There was lower effectiveness against milder disease. Further studies should continue to report effectiveness against AGE and less-severe rotavirus disease because as evidenced by pre-vaccine introduction studies this is likely to contribute the greatest burden on healthcare resources, particularly in high income countries.

3.2 Background

Prior to the introduction of rotavirus vaccine into childhood immunisation schedules, rotavirus was the most common cause of severe gastroenteritis in infants and young children. Thus, rotavirus gastroenteritis (RVGE) was estimated to be responsible for 453,000 deaths worldwide in children under 5 years of age in 2008, with over 90% of deaths occurring in low income countries (12). The global morbidity from rotavirus infection was also substantial with pre-vaccine introduction studies indicating that approximately 40% of diarrhoeal hospitalisations in children were caused by rotavirus (164). In middle and high income countries without vaccination the burden of RVGE remains substantial in infants and young children with high rates of disease and rotavirus the major contributor to diarrhoea hospitalisation. In the UK prior to vaccine introduction RVGE was estimated to be responsible for 45%

of acute gastroenteritis (AGE) hospital admissions, 80,000 primary care consultations and 750,000 annual diarrhoeal episodes in children under 5 years of age (29,30). In middle-income countries such as, Mexico and Peru, prior to vaccine introduction the average incidence of RVGE was 0.3 episodes per child per year in children <2 years, resulting in significant healthcare use and mortality (165). Although the majority of severe RVGE occurs among young children, older children and adults can be affected, however rotavirus infection often causes milder symptoms or is asymptomatic in these ages, meaning the true burden and rate of disease incidence is poorly understood.

Since improvements in sanitation and hygiene are not expected to substantially reduce the incidence of rotavirus infection, and treatment of RVGE is limited to rehydration therapy, immunisation of infants is considered the best option for control of the global burden of rotavirus disease (49,54,51). Since 2006 there have been two live-attenuated oral rotavirus vaccines that are licensed for use globally. A two dose monovalent vaccine (Rotarix®, GlaxoSmithKline Biologicals, Belgium), with the first dose typically administered at between 6-8 weeks of age and a second dose at least 4 weeks later and a three dose pentavalent vaccine (RotaTeq®, Merck), administered at 6-12 weeks of age with subsequent doses at 4-10 week intervals. Randomised controlled trials (RCTs) demonstrated both vaccines to be efficacious against severe RVGE; vaccine efficacy of over 80% has been shown in middle- and high-income countries, whilst trials in low-income settings have reported efficacy against severe RVGE of 40-60% (61). These trials led to a World Health Organisation (WHO) recommendation for universal vaccination of all children (12,166). More than 90 countries have since adopted rotavirus vaccination and the global mortality from RVGE is estimated to have fallen to 215 000 in 2013, with

almost 50% of deaths occurring in four lower-income countries (73,124). Currently within the European Union only nine countries include rotavirus vaccination in their childhood immunisation programme (140,167).

It is now a decade since the licensing and first introduction of rotavirus vaccination into childhood vaccination schedule. In order to inform immunisation policy, we have conducted a systematic review and meta-analysis of the literature on observational studies in order to assess the population effectiveness of the Rotarix® and RotaTeq® against RVGE. Effectiveness was examined by severity and by region.

3.3 Methods

3.3.1 Inclusion / exclusion criteria

We included prospective or retrospective observational studies (cohort and case-control studies) reporting the population effectiveness of the monovalent Rotarix® (RV1) or pentavalent RotaTeq® (RV5) against healthcare attendance for RVGE or other AGE in countries where the vaccines are included in the national immunisation programme or privately offered through medical insurance. Studies published between January 2006 and 28th April 2014 were eligible for inclusion. Review articles, editorials and conference abstracts were included in citation checking but excluded from final analysis. Randomised controlled trials were also excluded.

3.3.2 Search strategy

We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. We systematically searched PubMed, Medline, Web of Science, Cinhal and Academic Search Premier, OpenGrey and the Cochrane Library databases using a well-defined search strategy following a protocol registered on the University of York database for Prospectively Registered

Systematic Reviews (PROSPERO: 2014:CRD42014012974). A number of relevant organisations websites were also systematically searched, and included the WHO, Public Health England, and Centers for Disease Control and Prevention. We systematically searched the literature by, pairing the terms [vacc*] and [rotavirus] with the following key words: [immuni*], [effect*], [evaluation], and [efficacy].

Authors (DH and CM) replicated the search strategy and independently screened titles and abstracts to identify full studies that were eligible for full publication review. Subsequently these two authors independently assessed the full text publications and their final inclusion was based on a consensus between the reviewers (DH, CM, KS, AT).

3.3.3 Data extraction

Data extraction was autonomously carried out by three authors (DH, AT, KS) and a collaborator (MSC) using a pre-designed internally piloted extraction tool. For each study the following information was extracted: Author, Year of publication, country and region of study, funding source, study period, country vaccine coverage, study type, sample size, age of subjects, type of vaccine (RV1 and / or RV5) in case and controls groups, case definition, control definition, number of vaccine doses, relative risks / risk ratios (RR) or odds ratio (OR) or vaccine effectiveness (VE) and 95% confidence intervals (95% CI) and, if applicable, a measure of intussusception.

3.3.4 Grading of selected studies

The Newcastle-Ottawa Scale (NOS) for assessing the quality of non-randomised studies was identified as an appropriate tool to assess study quality (168). Case-control and cohort-studies were assessed using the tool by the same three researchers that carried out data extraction. To quality assess case-control studies the scale used: 1) adequate definition of a case and the representativeness of cases; 2) controls

selection and case definition; 3) matching of controls or adjustment for confounders in analysis; 4) ascertainment of method of cases and controls in terms of exposure (rotavirus vaccination) and non-response rate. To quality assess cohort-studies the factors assessed were: 1) representativeness of the vaccinated cohort and selection of unvaccinated cohort in relation to the vaccinated; 2) ascertainment of vaccination record, confirmation of rotavirus negative at start of study; 3) matching of exposed and non-exposed in design or adjustment for confounders in analysis; 4) ascertainment of outcome (rotavirus infection); 5) follow-up duration in relation to outcome appearance (e.g. 1 year from vaccination date) and was follow-up adequate (we defined adequate as ascertainment of outcomes for >80% of participants). The scale is categorised into three groups, selection, comparability and outcome / exposure; a maximum of nine stars can be awarded to each study. Studies scoring 0 in any of the categories were classified as having a high risk of bias, studies scoring 1 in any categories (moderate risk of bias) and 2 or above in all categories (low risk of bias).

3.3.5 Statistical analysis

We used Stata, version 14, statistical software (Stata Corp., College Station, TX, USA) to perform all statistical calculations for this meta-analysis. Meta-analyses were conducted separately for cohort and case-control studies. We used the study published RR for cohort studies and OR for case-control studies and calculated standard errors (SE) using study reported confidence intervals in the formula:

$$SE = \frac{ln(Upper\ confidence\ interval) - ln(Lower\ Confidence\ interval)}{3.92}$$

Where studies did not report OR or RR, authors calculated crude OR or RR and SE using reported numbers of cases and controls. When a study reported both

unadjusted and adjusted RRs / ORs, adjusted RRs / ORs were included in meta-analysis and unadjusted estimates excluded. Vaccine effectiveness was defined as $100 \times (1 - RR)$ or $100 \times (1 - OR)$. A random effects model was used to provide pooled estimates of VE. Because of differences in reported vaccine efficacy a decision was taken during data extraction, for analyses to be stratified by country income category, as defined by the World Bank and measured using gross national income per capita (61,169). Where a study had reported VE for multiple years the estimate for mid or most recent year (if only two years) were included in the meta-analysis. Heterogeneity was measured using chi-squared (χ^2) heterogeneity p-values and I^2 statistics. A p-value<0.1 was considered to identify statistically significant heterogeneity rather than 0.05 due to the small number of studies included. The percentage of variance across studies due to heterogeneity rather than chance was categorised as low, moderate and high using I^2 values of 25-49%, 50-74% and >=75%, respectively (170).

Sensitivity analysis was conducted based on the NOS score, excluding studies with a high or moderate risk of bias and assessing whether a study was conducted in a country with routine vaccination (part of recommended health policy) or in countries where vaccination provision is private or only available in some states. Subgroup analysis was conducted on: number of doses (1 dose, and full doses), age group, and vaccine type. Both number of doses and vaccine type were identified as important analyses post-hoc. Where studies reported more than one type of control group the following hierarchy was used to select estimates for use in meta-analyses: 1) community / neighbourhood; 2) hospital non-AGE controls; hospital rotavirus negative AGE controls. Publication bias was checked by funnel plot asymmetry and use of Begg's test (171).

3.4 Results

3.4.1 Study characteristics

The initial search strategy identified 2,097 studies as potentially relevant; of these, 30 were eligible for inclusion in the review (Figure 3-1) (85,172–200).

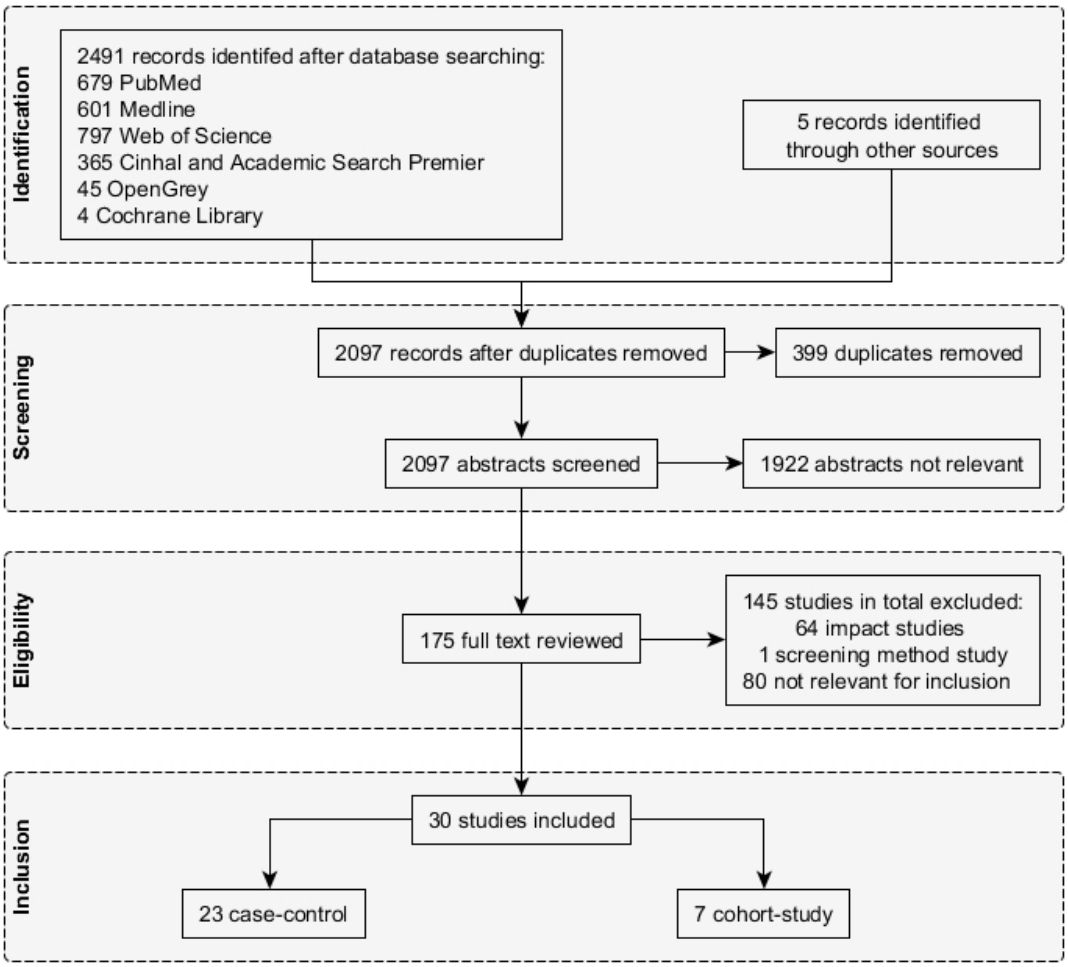

Figure 3-1 Flow chart of publications included and excluded for this review

Summary tables of study characteristics are available in Appendix C. Seven studies were cohort studies and 23 were case-control studies (Table 3-1 and Table 3-2). Nineteen were from high-income countries and eleven were from middle-income countries. Seven studies declared some funding from industry related to the rotavirus vaccines under study. Over a third of studies were conducted in the USA (n=12). The majority of studies (27/30) reported on RVGE hospitalisations and / or emergency department (ED) attendances for AGE with a positive laboratory test for

rotavirus. A study by Mast et al., (172) measuring VE against RVGE hospitalisation and ED attendances included only cases with severe disease defined by a Vesikari score of greater than 11 in their VE estimate (62,172,201). Two studies reported RVGE ED attendances and hospitalisations combined. Five studies included community consultations for either RVGE or AGE (173–177), which included a range of definitions including outpatient, physician and telephone consultation.

Controls for case-control studies were primarily hospital controls that were admitted for AGE symptoms but with a rotavirus negative laboratory test result. A few studies also used community asymptomatic controls or non-AGE hospital controls, such as children admitted with acute respiratory infection (Appendix C: Table S2). VE was measured for a range of age groups across studies.

The study by Fontes Vieira et al. 2011 conducted in Brazil on a community cohort examined VE against laboratory confirmed RVGE but did not report an estimate of VE; a crude estimate was therefore calculated by the authors (173). In the majority of studies, laboratory confirmation of RVGE followed hospitalisation, an ED attendance or GP consultation for gastroenteritis symptoms such as diarrhoea. Study selection identified five studies from countries (Spain and Israel) where routine childhood vaccination is not available but either the monovalent or pentavalent vaccine is available privately and / or only in some states (174,178,180,186,197).

Table 3-1 Cohort studies estimating vaccine effectiveness against hospitalisations, emergency department attendances and community consultations for RVGE or AGE

Study	Country	Vaccine	Age (months)	Cohort year	Vaccinated (N)		Unvaccinated (N)	Vaccine effectiveness (95% CI)	
					Dose	Incidence	Incidence	Unadjusted	Adjusted
Hospitalisation for RVGE									
Eberly 2011 (179)	USA	RV1 and RV5	<60	All	1	NR	581/237660	86 (78-91)	NR
					1 or more	42/140213		88 (83-91)	NR
					2 RV1 / 3 RV5	11/NR		90 (82-95)	NR
Panozzo 2014* (85)**]**	USA	RV1 and RV5	8-20	1	1 or more	3/68380	60/64929	NR	87 (58-96)
				2		23/175890	91/91051	NR	87 (80-92)
				3		22/250035	74/61218	NR	92 (87-95)
				4		8/254377	13/41946	NR	90 (75-96)
Hospitalisation and ED attendance for RVGE									
Wang 2010 (176)	USA	RV5	<36	All	3	0/7700	23/5831	100 (87-100)	NR
Wang, 2013 (177)	USA	RV5	<36	All	1	2/5019	11/3343	88 (45-99)	NR
				All	2	1/5886	13/4432	94 (61-100)	NR
Hospitalisation and ED attendance for AGE									
Wang 2010 (176)**]**	USA	RV5	<36	All	3	87/7700	160/5831	59 (46-69)	59 (47-68)
Wang, 2013 (177)**]**	USA	RV5	<36	All	1	53/5019-	63/3343	44 (18-62)	46 (22-63)
				All	2	78/5886	98/4432	40 (18-56)	39 (16-55)
Hospitalisation for AGE									
Panozzo 2014* (85)**]**	USA	RV1 and RV5	8-20	1	1 or more	142/68378	271/64928	NR	22 (3-37)
				2		413/175765	317/90882	NR	40 (30-48)
				3		512/249838	300/61136	NR	56 (49-62)
				4		398/254232	109/41888	NR	41 (27-53)
Community consultations for RVGE									
Wang 2010 (176)**]**	USA	RV5	<36	All	3	1/7700	20/5831	96 (76-100)	NR
Wang 2013 (177)**]**	USA	RV5	<36	All	1	0/5019 -	7/3343	100 (54-100)	NR
				All	2	4/5886	5/4432	40 (<0-88)	NR
Community consultations for AGE									
Fontes-Vieira 2011 (173)****	Brazil	RV1	<12	1	2	87/100	84/100	-4 (-16 to 8)	NR
				2		52/100	42/100	-24 (-67 to 8)	NR
Muhsen 2011 (174)**]**	Israel	RV1	<12	All	1	153/716	8801/18591	54 (47-60)	NR
				All	2	1605/6870		50 (47-52)	NR
Nolan 2012 (175)†	USA	RV5	<24	1	1 or more	NR	NR	NR	28 (-21 to58)
				1		NR	NR	NR	22 (-13 to 46)
				2		NR	NR	NR	37 (-37 to 71)
Wang 2010 (176)**]**	USA	RV5	<36	All	3	1321/7700	1377/5831	27 (22-33)	28 (22-33)
Wang 2013 (177)**]**	USA	RV5	<36	All	1	651/5019	521/3343	17 (6-26)	17 (7-26)
				All	2	774/5886	847/4432	31 (24-38)	28 (21-35)

* Direct effect estimates, ** Crude VE calculated by authors, *NR* not reported, *ED* emergency department, *d* days, *AGE* acute gastroenteritis, *RVGE* rotavirus gastroenteritis, †GP consultations reported, paper also reported telephone triage and episodes (calls and visits within ten days), two cohorts were followed, the 1st for two seasons and 2nd for one season

Table 3-2 Case-control studies estimating vaccine effectiveness against hospitalisations, ED attendances for RVGE or AGE [partial: 1 dose of RV1 or RV5]

Study	Country	Vaccine	Age months (m) or days (d)	Control group	Cases vaccinated (n/N)		Controls vaccinated (n/N)		Vaccine effectiveness (95% CI)	
					Partial	Full	Partial	Full	Partial	Full
Hospitalisations for RVGE										
Braeckman 2012 (187)	Belgium	RV1	<36	Hospital - RV (-) AGE	81/179*	70/160	208/228	179/198	91 (82-95)	90 (81-95)
			3-11		36/77*	30/66	99/104	79/84	93 (80-97)	91 (75-97)
			12-31		45/102*	40/94	109/124	100/114	89 (75-95)	90 (76-96)
Carvalho-Costa 2009 (181)**]**	Brazil	RV1	<60	Hospital - RV (-) AGE	NR	4/14	NR	35/60	NR	71 (-15-93)
Castilla 2012 (186)**]**	Spain	RV1 & RV5	3-59	Hospital - RV (-) AGE	NR	9/262	NR	80/518	NR	83 (65-93)
			<24		NR	8/215	NR	69/371	NR	82 (60-93)
			24-59		NR	1/43	NR	11/99	NR	89 (17-99.8)
Correia 2010 (190)	Brazil	RV1	6-11	Hospital - RV (-) AGE	NR	NR	NR	NR	NR	77 (42-91)
Cortese 2011 (191)	USA	RV5	>7	Hospital - RV (-) AGE	NR	20/140	NR	163/280	NR	92 (86-96)
			>7	Community[a]	NR	17/221	NR	672/1953	NR	90 (84-94)
Cortese 2013 (192)**]**	USA	RV1	>7	Hospital - RV (-) AGE	NR	2/30	NR	101/140	NR	98 (90-100)
			>7	Community[a]	NR	2/28	NR	206/440	NR	94 (71-99)
Cotes-Cantillo 2014 (185)**]**	Colombia	RV1	<60	Hospital - RV (-) AGE	NR	6/84	NR	670/711	NR	-2 (-182 to 63)
			6-11		NR	12/15	NR	628/655	NR	84 (23-97)
			≥12		NR	64/67	NR	628/655R	NR	-80 (-559 to 51)
de Palma 2010 (193)	El Salvador	RV1	<25	Community	72/171	152/251	199/352	617/770	51 (26-67)	76 (64-84)
			6-11		NR	49/63	NR	205/222	NR	83 (68-91)
			12-24		NR	79/108	NR	284/335	NR	59 (27-77)
Desai 2010 (194)	USA	RV1 & RV5	2-35	Hospital - RV (-) AGE	5/42*	NR	24/80	NR	94 (55-99)	NR
				Community	5/42*	NR	21/73	NR	96 (59-99.8)	NR
Guh 2011 (195)**]**	USA	RV5	<36	Community	2/54	0/54	34/270	25/270	84 (25-96)	92 (48-100)
Ichihara 2014 (196)**]**	Brazil	RV1	4-24	Hospital – RV (-) and non-vaccine preventable	33/215	115/215	279/1961	1481/1961	60(37-75)	72(44-85)
Justino 2011 (188)*****	Brazil	RV1	3-11	Hospital - non AGE or vaccine preventable	NR/120	NR/77	NR/120	NR/77	61 (28-78)	56 (12-78)
			12-35		NR/324	NR/235	NR/324	NR/235	35 (4-56)	32 (-4 to 46)
			3-35		NR/444	NR/312	NR/444	NR/312	44 (23-60)	40 (14-58)
			3-11	Community no AGE symptoms	NR/91	NR/64	NR/91	NR/64	89 (63-97)	96 (68-99)
			12-35		NR/240	NR/185	NR/240	NR/185	48 (17-68)	65 (37-81)
			3-35		NR/331	NR/249	NR/331	NR/249	62 (42-75)	76 (58-86)
Muhsen 2010 (197)*****	Israel	RV1 & RV5	<28 (approx.)	Hospital - RV (-) AGE	2/111	NR	36/216	NR	89 (52-98)	NR
Martinon-Torres 2011 (180)	Spain	RV1 & RV5	<24	Hospital - RV (-) AGE	2/75	1/74	22/186	130/294	80 (11-95)	98 (87-99.8)
Patel 2009	Nicaragua	RV5	<24	Community	31/80	143/192	116/213	442/539	52 (14-	43 (9-

Study	Country	Vaccine	Age months (m) or days (d)	Control group	Cases vaccinated (n/N)		Controls vaccinated (n/N)		Vaccine effectiveness (95% CI)	
					Partial	Full	Partial	Full	Partial	Full
(182)									73)	64)
				Hospital - RV (-) AGE	31/80	143/192	106/181	350/425	60 (24-78)	49 (17-68)
				Community and Hospital - RV (-) AGE	31/80	143/192	222/394	792/964	55 (22-74)	44 (15-63)
Patel 2013 (198)	Bolivia	RV1	6-11	Hospital - RV (-) non AGE	NR	NR	NR	NR	NR	77 (51-89)
			12-35		NR	NR	NR	NR	NR	76 (59-86)
			<36		100/192	208/300	226/343	857/974	56 (32-72)	77 (65-84)
			6-11	Hospital - RV (-) AGE	NR	NR	NR	NR	NR	64 (34-80)
			12-35		NR	NR	NR	NR	NR	72 (52-86)
			<36		100/192	208/300	131/208	510/587	36 (0-59)	69 (54-79)
Patel 2012 (183)	Nicaragua	RV5	6-44	Hospital - RV (-) Non AGE or vaccine preventable and Community	NR	773/849	NR	3914/4062	NR	70 (59-78)
			6-11		NR	NR	NR	NR	NR	73 (54-84)
			12-44		NR	NR	NR	NR	NR	68 (51-79)
			6-44	Hospital - RV (-) AGE	NR	773/849	NR	3097/3247	NR	45 (25-59)
			6-11		NR	NR	NR	NR	NR	64 (43-78)
			12-44		NR	NR	NR	NR	NR	30 (-5 – 53)
Payne 2013 (184)**]**	USA	RV1	<60	Hospital - RV (-) AGE	NR/22	NR	NR/34	NR	32 (-156-82)	NR
		RV5			NR/130	NR	NR/372	NR	86 (74-91)	NR
Snelling 2009 (199)**]**	Australia	RV1	<60	Community	10/21	3/21	58/83	32/83	57 (<0-83)	85 (23-97)
Staat 2011 (189)**]**	USA	RV5	1-37	Hospital - RV (-) AGE	1/38	3/40	12/44	17/49	89 (16-99)	95 (48-99)
			1-37	Hospital - RV (-) ARI	1/60	29/102	5/64	40/113	94 (55-99)	82 (50-93)
Hospital admissions for AGE										
Snelling 2009 (199)	Australia	RV1	<60	Community	21/42	11/42	120/166	72/166	67 (29-84)	78 (40-92)
ED attendances for RVGE										
Cotes-Cantillo 2014 (185)**]**	Colombia	RV1	<60	ED - RV (-) AGE	NR	143/156	NR	670/711	NR	16 (79-61)
			6-11		NR	27/31	NR	27/655	NR	79 (24-94)
			≥12		NR	112/119	NR	628/655	NR	-40 (-271 to 47)
Cortese 2011 (191)**]**	USA	RV5	>7	Hospital- RV (-) AGE	NR	8/41	NR	163/280	NR	81 (53-92)
			>7	Community	NR	6/62	NR	138/567	NR	84 (58-94)
Cortese 2013 (192)	USA	RV1	>7	Hospital- RV (-) AGE	NR	20/65	NR	101/140	NR	86 (67-94)
			>7	Community	NR	17/61	NR	438/862	NR	65 (35-81)
Payne 2013 (184)**]**	USA	RV1	<60	ED- RV (-) AGE	38	NR	121	NR	78 (46-91)	NR
		RV5	<60	ED- RV (-) AGE	229	NR	1439	NR	81 (70-84)	NR
Staat 2011 (189)	USA	RV5	15 d-47m	ED- RV (-) AGE	5/56	8/59	12/66	22/76	75 (-64 -96)	74 (16-92)
			15 d-47m	ED - ARI	7/76	8/77	16/101	54/139	45 (-80 -83)	88 (64-96)
Hospitalisations and ED attendances for RVGE										
Cortese 2011 (191)**]**	USA	RV5	>7	Hospital RV (-) AGE	10/163	23/283	20/137	141/341	69 (27-87)	89 (81-94)
			8-11		NR	4/24	NR	63/92	NR	93 (75-99)

Study	Country	Vaccine	Age months (m) or days (d)	Control group	Cases vaccinated (n/N)		Controls vaccinated (n/N)		Vaccine effectiveness (95% CI)	
					Partial	Full	Partial	Full	Partial	Full
			12-23		NR	21/102	NR	86/147	NR	89 (77-94)
			>23		NR	3/55	NR	14/41	NR	91 (62-99)
			56d-5m		11/69	NA	97/248	NA	71 (40-87)	NA
			56d-5m	Community[a]	11/69	NA	184/633	NA	62 (20-82)	NA
			>7		NR	23/283	NR	850/2520	NR	89 (83-93)
			8-11		NR	3/109	NR	194/1009	NR	94 (78-99)
			12-23		NR	17/116	NR	517/988	NR	88 (80-93)
			>23		NR	3/58	NR	139/523	NR	87 (56-96)
Cortese 2013 (192)**]**	USA	RV1	>7	Hospital RV (-) AGE	NR	22/95	NR	101/140	NR	91 (80-95)
			8-11		NR	5/14	NR	45/61	NR	85 (35-97)
			12-23		NR	14/66	NR	46/68	NR	91 (75-96)
			>7	Community[a]	NR	19/89	NR	644/1302	NR	76 (58-86)
			8-11		NR	4/14	NR	114/196	NR	70 (24-91)
			12-23		NR	13/65	NR	462/967	NR	76 (53-87)
Donauer 2013 (200)**]**	USA	RV5	<36	Community	8/76	2/76	165/743	329/743	77 (14-94)	92(60-99)
				Hospital - RV (-) AGE	8/76	2/76	47/179	15/179	68 (-18 to 91)	92(21-99)
				Hospital - RV (-) ARI	8/76	2/76	71/288	27/288	58 (-38 to 87)	92(33-99)
Mast 2011 (172)**]**	Nicaragua	RV5	Overall	Community	NR	241/300	NR	812/851	NR	87(74-93)
			<12		NR	62/84	NR	219/225	NR	93(62-99)
			≥ 12		NR	179/216	NR	593/626	NR	85(69-93)
			Overall	Hospital – RV(-) AGE	NR	241/300	NR	711/792	NR	64(44-78)
			<12		NR	62/84	NR	215/233	NR	78(49-91)
			≥ 12		NR	179/216	NR	496/559	NR	55(22-74)
			Overall	Combined	NR	241/300	NR	1523/1643	NR	76(63-84)
			<12		NR	62/84	NR	434/458	NR	85(66-93)
			≥ 12		NR	179/216	NR	1089/1185	NR	71(51-82)
Payne 2013 (184)**]**	USA	RV1	<60	Hospital - RV (-) AGE	46	56	83	140	57 (-45-87)	70 (39-86)
			12-23		7	NR	54	-	56 (-59-100)	NR
			24-35		46	NR	79	NR	86 (60-95)	NR
		RV5	<60	Hospital - RV (-) AGE	233	537	307	1445	70 (50-82)	84 (78-88)
			12-23		34	NR	402	NR	85 (63-94)	NR
			24-35		121	NR	681	NR	89 (82-93)	NR
			36-47		91	NR	414	NR	83 (69-90)	NR
Staat 2011 (189)**]**	USA	RV5	15d - 37m	Hospital - RV (-) AGE	9/136	16/143	40/191	87/238	74 (37-90)	87 (71-94)
			1-11		6/65	3/62	30/109	19/98	63 (7-87)	86 (31-97)
			12-23		3/38	8/43	6/45	48/87	81 (22-97)	90 (65-97)
			15d - 37m	Hospital - RV (-) ARI	10/159	17/166	79/391	195/507	73% (43-88)	85 (72-91)

Study	Country	Vaccine	Age months (m) or days (d)	Control group	Cases vaccinated (n/N)		Controls vaccinated (n/N)		Vaccine effectiveness (95% CI)	
					Partial	Full	Partial	Full	Partial	Full
			1-11		6/76	3/73	60/230	43/213	74 (31-90)	84 (41-96)
			12-23		4/41	9/46	15/87	104/176	70 (16-92)	87 (68-95)
Any episode of RVGE										
Bellido-Blasco 2012 (178)**]**	Spain	RV1 & RV5	<36	RV (-) AGE	2/71	NR	57/261	NR	88 (46–99.7)	NR
Castilla 2012 (186)**]**	Spain	RV1 & RV5	3-59	RV (-) AGE	45/756*	34/756	1094/6036*	849/6036	78 (70-84)	78 (68-85)
			3-11		NR	12/309	NR	248/1365	NR	78 (58-88)
			12-23		NR	16/318	NR	481/2678	NR	82 (69-89)
			24-59		NR	6/118	NR	120/1748	NR	61 (0-84)
Martinon-Torres 2011 (180)**]**	Spain	RV1 & RV5	<24	RV (-) AGE	3/143	8/148	22/186	130/294	84(46-95)	93

AGE, all cause gastroenteritis symptoms; ARI, acute respiratory infection; RV (-), rotavirus test negative; ED, emergency department; d, days. *One or more doses reported for partial

3.4.2 Quality of included observational studies

The quality of studies varied considerably (Table 3-3). It was difficult to ascertain for most studies whether history of disease in control subjects was considered. The majority of studies used a combination of vaccination cards and medical records to ascertain vaccination status. The majority of studies either matched controls or adjusted for age in the analysis as a minimum and those with community controls often used an indicator of residence such as GP location as a covariate. A high risk of bias was identified in two out of seven cohort studies (173,179) and two out of 23 case-control studies had a high risk of bias (180,181).

Table 3-3 Quality of observational studies included in the review of rotavirus vaccine effectiveness

Study	Country	Study design	Selection	Comparability	Outcome / exposure	Overall	Bias
Bellido-Blasco 2012 (178)	Spain	Case-control	3	2	3	8	Low
Braeckman 2012 (187)	Belgium	Case-control	3	2	3	8	Low
Carvalho-Costa 2009 (181)	Brazil	Case-control	2	0	1	3	High
Castilla 2012 (186)	Spain	Case-control	3	2	3	8	Low
Correia 2010 (190)	Brazil	Case-control	3	1	3	8	Moderate
Cortese 2011 (191)	USA	Case-control	3	2	3	8	Low
Cortese 2013 (192)	USA	Case-control	3	2	3	8	Low
Cotes-Cantillo 2014 (185)	Colombia	Case-control	3	2	3	8	Low
de Palma 2010 (193)	El Salvador	Case-control	3	2	3	8	Low
Desai 2010 (194)	USA	Case-control	3	2	2	7	Low
Donauer 2013 (200)	USA	Case-control	2	2	2	6	Low
Guh 2011 (195)	USA	Case-control	4	1	3	9	Moderate
Ichihara 2014 (196)	Brazil	Case-control	3	2	2	7	Moderate
Justino 2011 (188)	Brazil	Case-control	4	2	3	9	Low
Martinon-Torres 2011 (180)]	Spain	Case-control	4	0	2	6	High
Mast 2011 (172)	Nicaragua	Case-control	3	2	1	7	Moderate
Muhsen 2010 (197)]	Israel	Case-control	3	2	1	6	Moderate
Patel 2009 (182)	Nicaragua	Case-control	4	2	3	9	Low
Patel 2012 (183)]	Nicaragua	Case-control	4	2	2	8	Low
Patel 2013 (198)	Bolivia	Case-control	3	2	3	8	Low
Payne 2013 (184)	USA	Case-control	3	2	2	7	Low
Snelling 2009 (199)	Australia	Case-control	3	2	3	8	Low
Staat 2011 (189)	USA	Case-control	3	2	2	7	Low
Eberly 2011 (179)	USA	Cohort	3	0	3	6	High
Fontes-Vieira 2011 (173)	Brazil	Cohort	3	0	2	5	High
Muhsen 2011 (174)	Israel	Cohort	3	1	3	7	Moderate
Nolan 2012 (175)	USA	Cohort	4	2	3	9	Low
Panozzo 2014 (85)	USA	Cohort	4	2	3	9	Low
Wang 2010 (176)	USA	Cohort	4	1	3	8	Moderate
Wang 2013 (177)	USA	Cohort	4	1	3	8	Moderate

3.4.3 Meta-analysis of vaccine effectiveness against hospitalisation or combined hospitalisation and emergency department attendance for RVGE

For this outcome measure cohort studies were too few to conduct a meta-analysis (Table 3-1). We therefore, included 21 out of the 22 case control studies that measured VE against hospitalisation or hospitalisation and ED attendance for laboratory confirmed RVGE in the meta-analysis. Patel et al. 2009 was excluded because a more recent publication Patel et al., 2012 provided more recent estimates of effectiveness for the same cohort (182,183). If studies reported more than one age group the overall estimate for the broadest age group was included in the meta-analysis. Studies which reported on 0 doses vs full dose or 0 dose vs 1+ dose were included. Some 22 estimates from 21 studies were included, as Payne et al, 2013 had separate results for RV1 and RV5 (184). The funnel plot shows some asymmetry, however this is not significant for Begg's (p=0.06) tests (Figure 3-2). Therefore, we included all 21 studies in the meta-analysis.

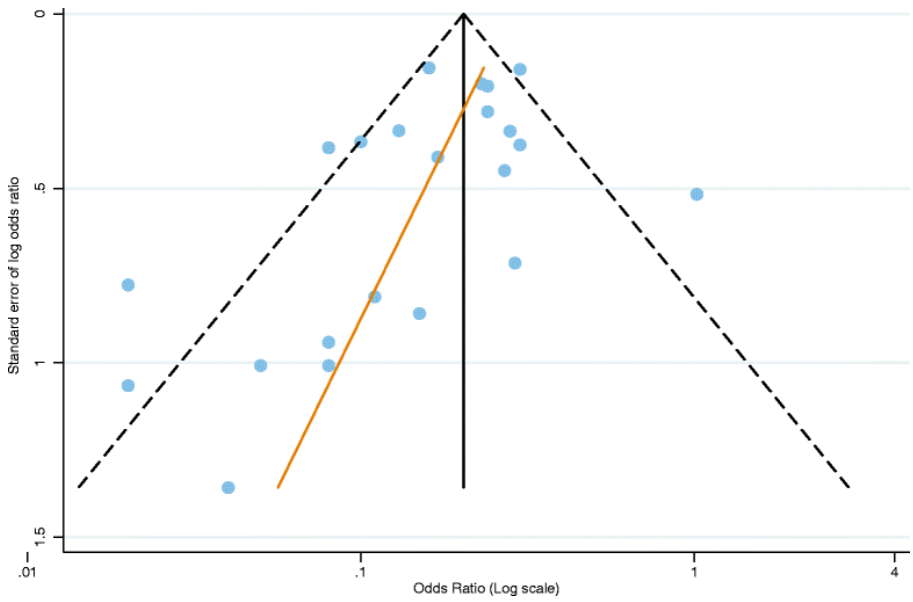

Figure 3-2 Funnel plot of vaccine effectiveness against hospitalisation or hospitalisation and emergency department attendance for RVGE [only adjusted effect estimates included]

There was statistically significant heterogeneity (I^2 = 60.6, p < 0.001) across all studies (Figure 3-3). Therefore pooled estimates of OR (0.18, 95% CI 0.14–0.23, 21 studies [22 estimates], p<0.001) were calculated using a random effects model. The pooled VE was therefore 82% (95% CI 77–86%; 21 studies [22 estimates], p<0.001). A stratified analysis by World Bank Country Classifications calculated pooled estimated ORs. Pooled VE was lower in middle-income countries (74% VE; 95% CI 67-80%; 9 studies, p<0.001) compared with high income countries (89% VE; 95% CI 84-92%; 12 studies [13 estimates], p<0.001). There was low to moderate heterogeneity for middle (I^2 = 37.4%, p=0.120) and high income countries (I^2 = 40.8%, p=0.06). The study by Cotes-Cantillo et al., 2014 was the only study to report a negative vaccine effectiveness (-2 VE; 95% CI -182 to 63%) (185).

Pooled estimates for case-control studies in high income settings (89% VE; 95% CI 84-92%; 12 studies [13 estimates]) were comparable to the three unpooled cohort study estimates. All cohort studies were conducted in high-income settings. One study reported an adjusted VE estimate of 87% (95% CI 80-92%) and other two studies stated unadjusted estimates of 100% (95% CI 87-100%), and 90% (95% CI 82-95%) (176,179,85).

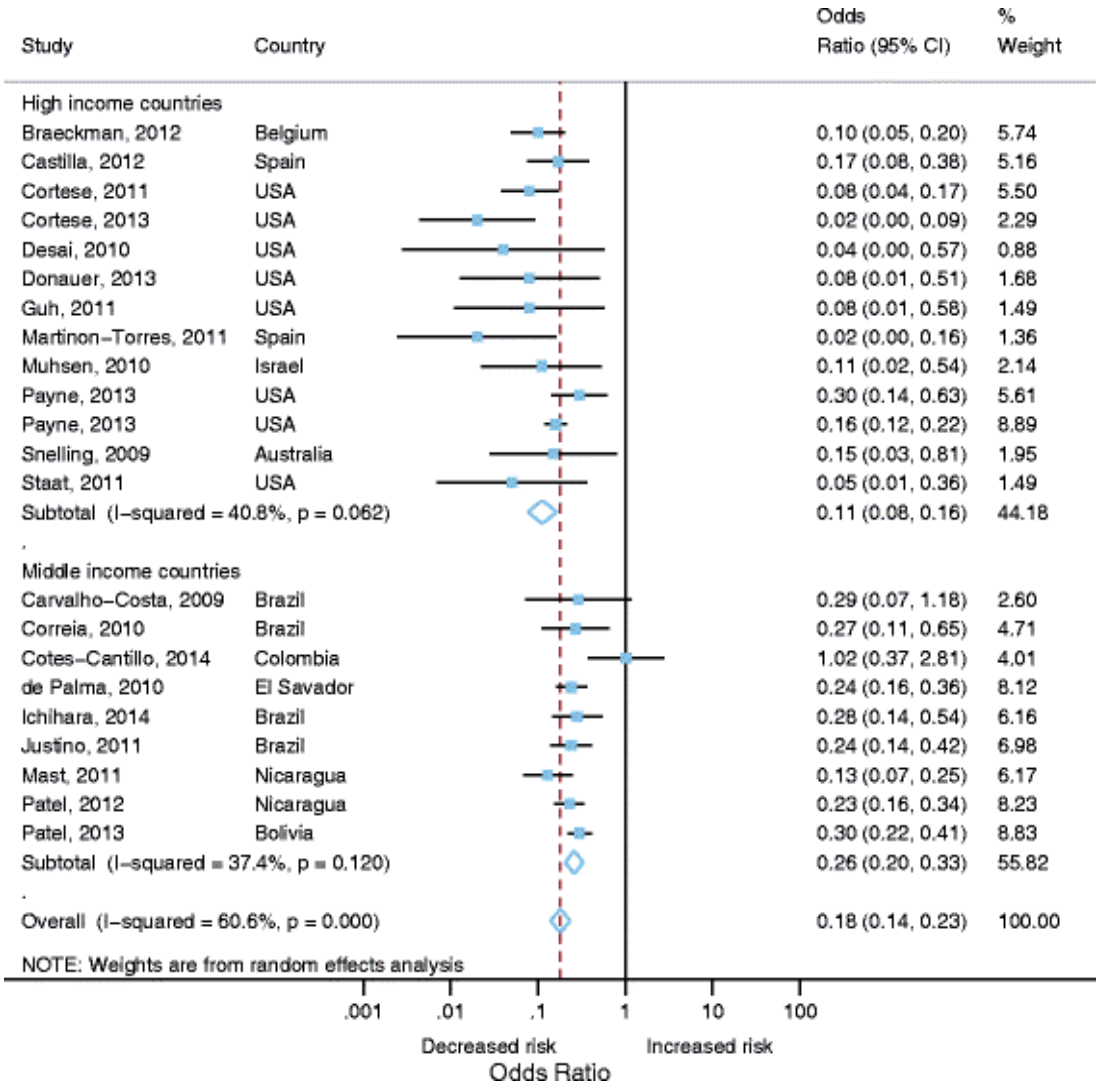

Figure 3-3 Vaccine effectiveness against hospitalisation or hospitalisation and emergency department attendance for RVGE [only adjusted effect estimates included]

Sensitivity analysis

We identified the possibility of study bias using the NOS. The pooled OR for studies with a low risk of bias was 0.18 (95% CI 0.13-0.25; 13 studies [14 estimates], p<0.001), suggesting that any bias in these studies may have been minimal. The corresponding pooled estimates by World Bank Country classification did not change substantially. When studies from countries with state-based or private rotavirus vaccine provision (Castilla et al 2012, Martinon-Torres, 2011 and Muhsen et al., 2010) were dropped from the meta-analysis the pooled OR remained similar (0.19 OR; 95% CI 0.14-0.25; 18 studies [19 estimates], p<0.001) (180,186,197).

To further investigate the potential for publication bias, specifically that the effect of industry funding, we excluded 4 studies which had measured RVGE hospitalisations but were funded by industry (172,187–189). Overall pooled ORs remained comparable (0.19 OR; 95% CI 0.14-0.26; 17 studies [18 estimates], p<0.001). We also established that including an estimate from a study which measured vaccine effectiveness against severe disease (Vesikari score ≥11), did not cause an overestimation of the pooled estimate (172).

Subgroup analyses

Age: Because the age groups included in studies were varied we grouped ages in to the following groups to assess VE by crude age groups: <1 year, <2 years, >1 year and 1-2 years of age. In middle-income countries there was some variation in pooled estimates by age group but confidence intervals overlapped between estimates (Figure 3-4a). Here estimates should be interpreted with caution as there was only 1 study in each of the 1-2 year and <2 year groups. Additionally, the VE estimate for children aged >12 months from the 2014 study by Cotes-Cantillo stood out as being

heterogeneous. As the authors note this is likely to be due to the low sample size in this group and potentially due to a variation in strain dominance by age (185). Estimates were very similar across age ranges in high income countries (Figure 3-4b).

Full v partial vaccine dose: To determine the impact of the number of vaccine doses on VE we compared studies which reported full dose vaccination with first dose vaccination for RV1 and RV5 VE estimates. There were 21 studies which either reported full or partial vaccination giving 32 estimates (13 partial schedule; 19 full vaccine schedule). Pooled VE for full dose (81% VE; 95% CI 75-86%, $p<0.001$) was higher than for partial dose (62% VE; 95% CI 55-69%, $p<0.001$). However, there was moderate to high heterogeneity for studies reporting estimates for full dose ($I2= 60.2\%$, $p<0.001$). When stratified by World Bank Country classification, this difference was most pronounced in middle-income countries, where pooled vaccine effectiveness for full dose was 74% (95% CI 67-80%, $p<0.001$) and 57% (95% CI 47-66%, $p<0.001$) for partial dose (Figure 3-5a). Wider CIs were reported in studies reporting full vaccination, likely due to smaller available sample sizes. In high-income countries VE for partial vaccine dose was 72% (95% CI 60-80%, $p<0.001$) compared to 87% (95% CI 81-91%, $p<0.001$) for full dose (Figure 3-5b).

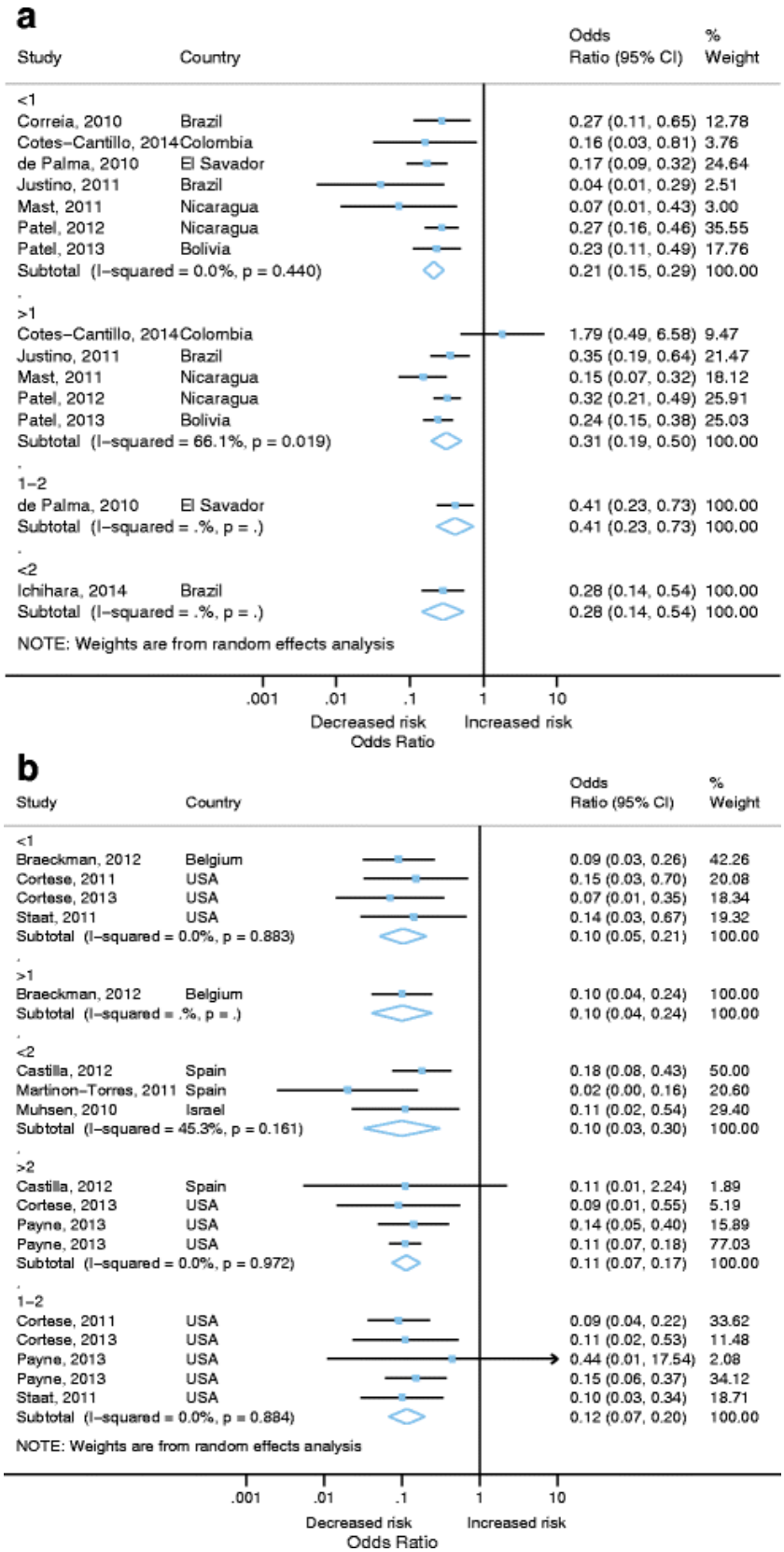

Figure 3-4 Vaccine effectiveness against hospitalisation or hospitalisation and emergency department attendance for RVGE comparing partial age groups a middle income countries, b high income countries [only adjusted effect estimates included]

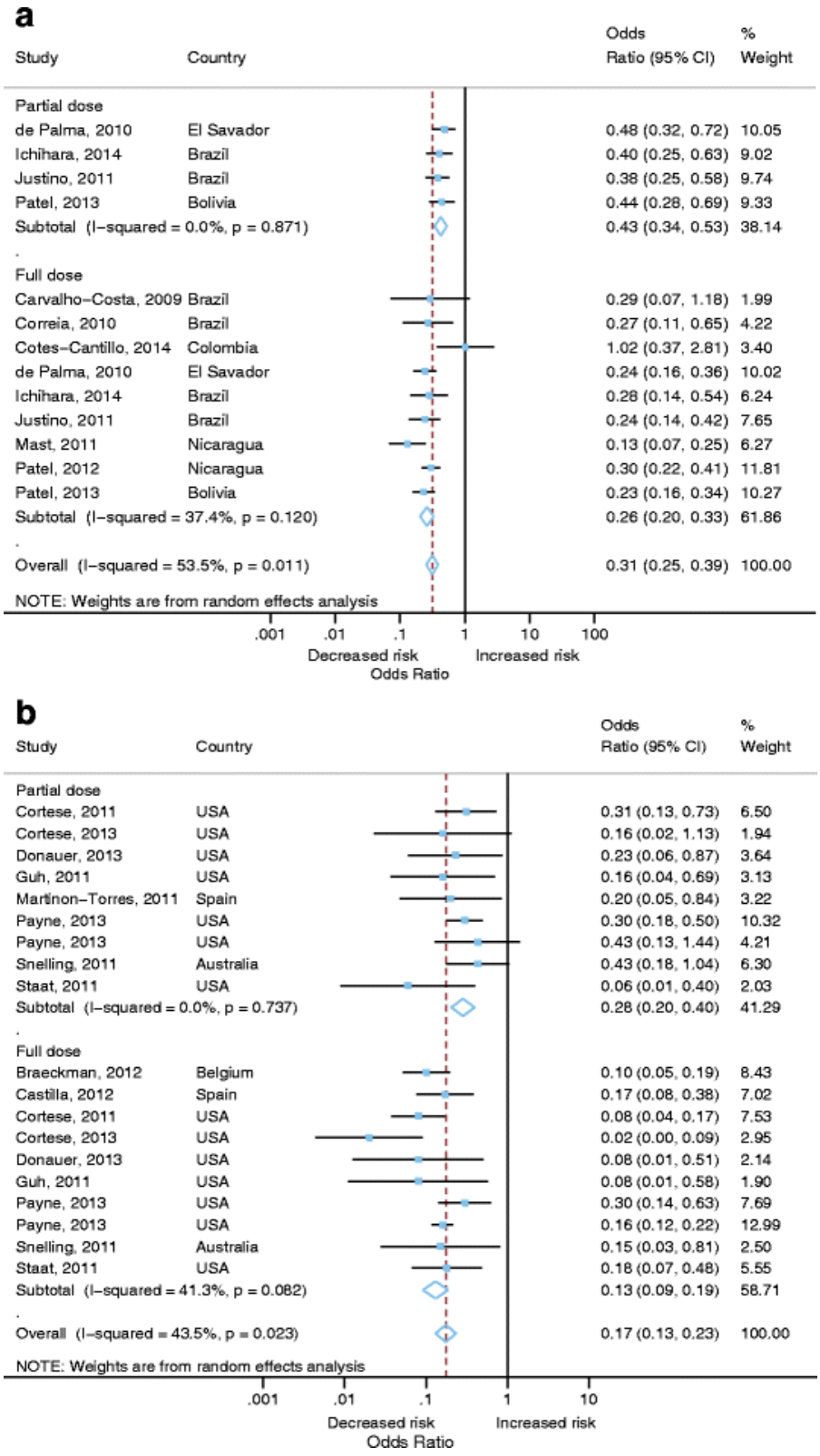

Figure 3-5 Vaccine effectiveness against hospitalisation or hospitalisation and emergency department attendance for RVGE comparing partial dose to full dose a) middle income countries, b) high income countries [only adjusted effect estimates included]

RV1 and RV5 vaccine effectiveness: Pooled VE for RV1 and RV5 stratified by World Bank Country classification showed that RV5 has slightly higher VE point estimates in both high and middle income countries but this difference was not significant. RV1 is the predominant vaccine used in studies from middle income countries included in the meta-analysis (7/10). In high income countries three studies reported VE for RV1, six for RV5 and four RV1 and RV5 combined.

3.4.4 Meta-analysis of vaccine effectiveness against emergency department attendances for RVGE

There were 4 estimates from three studies that included VE for ED attendances for RVGE (184,185,189). Three estimates were from high-income countries and one from middle-income. Publication bias was not assessed as there were inadequate numbers of studies to properly assess via a Begg's test. Heterogeneity was high for these studies (I^2 = 78.7%, p<0.001). Random effects meta-analysis gave a pooled OR of 0.26 (95% CI 0.12-0.57, p=0.001), indicating a significant effect of vaccination against ED attendances for RVGE (Figure 3-6). Analysis stratified by World Bank country classifications showed significant VE of 81% (95% CI 75-86%, p<0.001) for studies from high income countries. There was only one study from middle income countries with a VE of 16% (95% CI -79% to 61%, p=0.651).

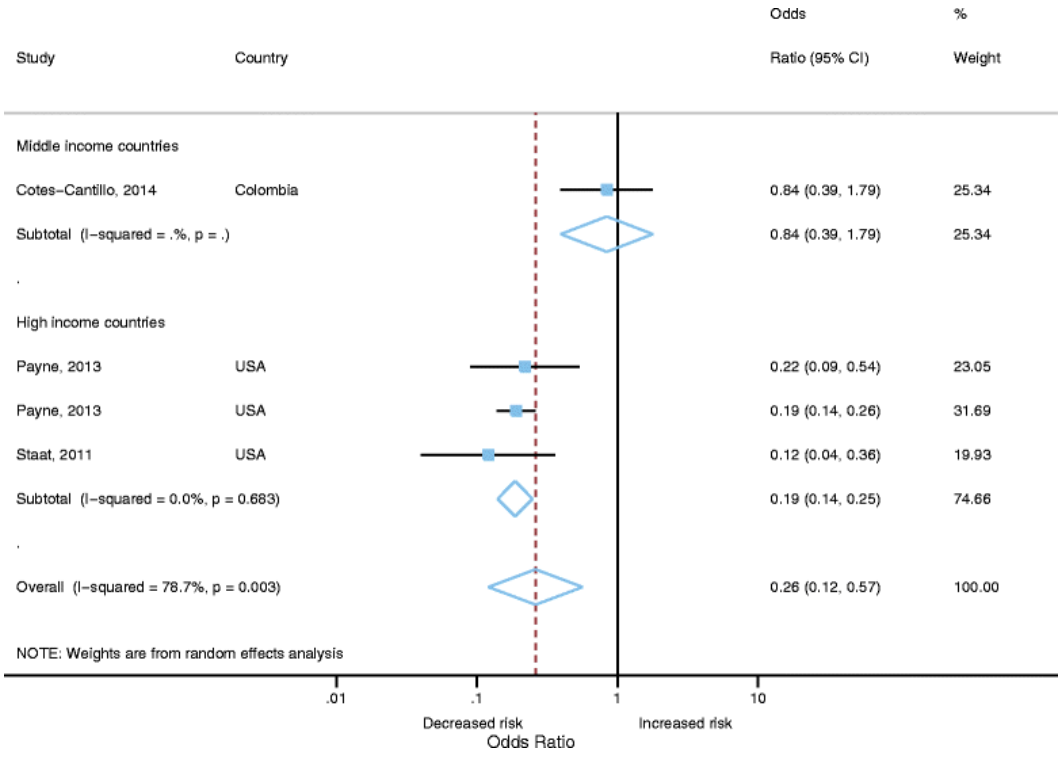

Figure 3-6 Vaccine effectiveness against emergency department attendances for RVGE [only adjusted effect estimates included]

3.4.5 Meta-analysis of vaccine effectiveness against community consultations for AGE

A single study reported full dose VE against community consultations for laboratory confirmed RVGE, reporting a high unadjusted VE estimate of 96% (95% CI 76-100%) (176,177). Four cohort studies included estimates of VE for community consultations for AGE (173–177). Three studies were from high-income countries and one from middle-income. Only two out of the four studies reported adjusted estimates. The study by Nolan et al., 2012 only reported an adjusted VE for 1 or more doses (175). We therefore could only include three cohort studies which report unadjusted VE in the meta-analysis. Publication bias was not assessed as there were inadequate numbers of studies to properly assess via a Begg's test. Heterogeneity was very high for these studies (I^2 = 97.9%, p<0.001). Random effects meta-analysis gave a pooled RR of 0.74 (95% CI 0.52-1.06, p=0.10), indicating a non-significant

effect of vaccination against community consultations for AGE (Figure 3-7). However, analysis stratified by World Bank Country classifications showed significant VE of 40% (95% CI 13-58%, p=0.008) for studies from high-income countries.

There was only one study from middle income countries with a VE of -24% (95% -67% to 8%, p=0.157), this study was assessed as having a high risk of bias as crude VE was calculated by the authors and children in the vaccinated cohort were significantly younger than the unvaccinated cohort.

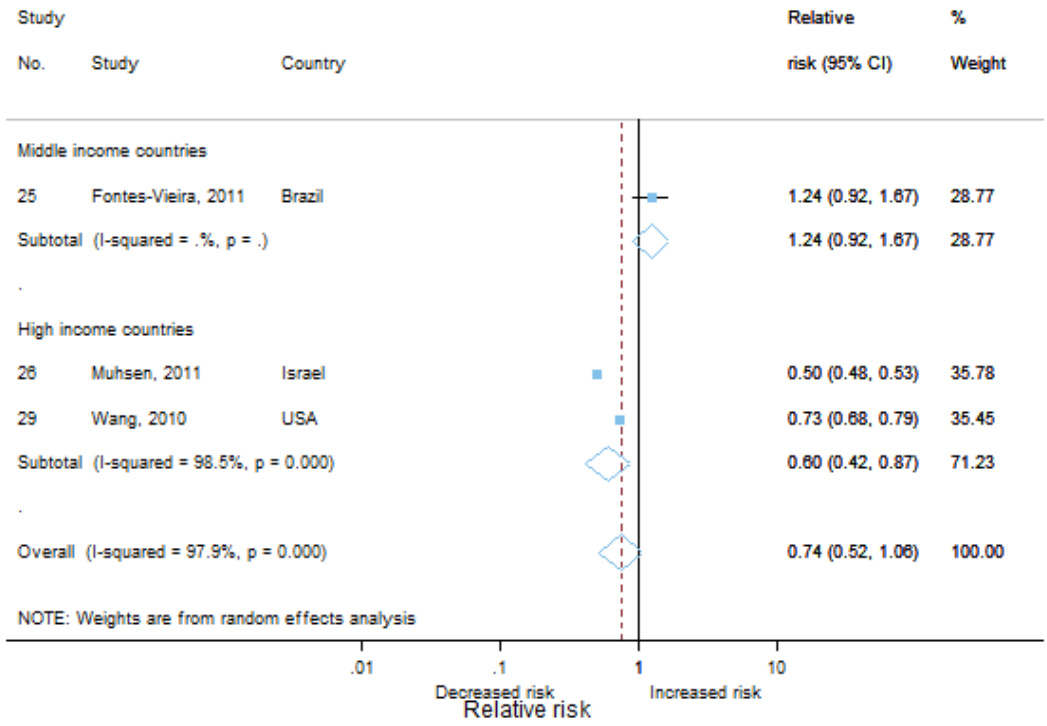

Figure 3-7 Vaccine effectiveness against community consultations for AGE [only unadjusted effect estimates included]

3.5 Discussion

The pooled data from case-control studies indicates that rotavirus vaccination is highly effective for preventing hospitalisations and / or ED attendances for laboratory confirmed rotavirus, as VE was 89% (95% CI 84-92) for high-income

countries and 74% (95% CI 67-80) for middle-income countries. This finding is further supported by comparable estimates from the unpooled cohort studies. Most studies reporting VE for community consultations could not identify the causative organism and therefore reported a much lower effectiveness against community consultations for AGE (26% VE; 95% CI -6 to 48%). However, like VE against RVGE hospitalisations and ED attendances, the pooled VE for community consultations for AGE was significant in high-income countries (40% VE; 95% CI 13-58%). This study was also able to show that studies from countries with similar economic classification demonstrate similar VE and that VE was lower in middle-income countries compared with high-income countries. Vaccine effectiveness against RVGE hospitalisations in high-income countries (89% VE; 95% CI 84-92%) was consistent with but at the upper limit of that reported in a Cochrane Review of RCTs; 85% (95% CI 80-88%) for RV1 and 82% (95% CI 50-93%) for RV5 for preventing severe rotavirus diarrhoea in children up to two years of age (61). Differing study definitions of severity and age may be responsible for the slight difference between pooled estimates. Additionally, pooled VE estimates from meta-analysis for RVGE hospitalisations in middle income countries (Brazil, Colombia, Nicaragua and Bolivia) were significantly lower than high income countries, again consistent with estimates from efficacy studies (61,67).

Our systematic review found substantial differences in the quality and design of studies and considerable heterogeneity. However, there was no evidence of publication bias. Heterogeneity was dealt with by stratifying the analysis by World Bank Country classification when heterogeneity was low to moderate and by using sensitivity analysis to identify factors which may have caused bias in the overall estimate. We conclude that the best pooled estimates are provided by stratifying by

World Bank country classification. Sensitivity analyses for RVGE hospitalisations and or ED attendances did not identify any substantial effects resulting from differences in study quality. Exclusion of studies from countries with only state based or private provision of rotavirus vaccination made little difference to the overall effect estimates.

Sub-analyses by vaccine dose identified that 1 dose of rotavirus vaccine conferred a lower overall VE estimate than full course dose, particularly in middle-income countries, indicating that there is a clear benefit for children completing the full schedule. Wider confidence intervals were seen for partial dose estimates due to smaller available sample sizes which are likely a result of the majority of children completing recommended schedules.

It was difficult to assess VE by age as the different studies reported VE for different age groups and therefore finding standard categorisations for age was problematic. Pooled VE estimates in children >1 year of age in middle-income countries were lower than for that for infants <1 year of age. This could be due to the higher relative disease burden in infants, a consequence of acquiring natural immunity with age, independent of vaccination (114). Nonetheless, classifications used here showed no significant differences between age groups in both high- and middle-income countries, suggesting that the RV vaccination is highly effective against RVGE hospitalisation regardless of age. Interestingly, one study from Colombia reported high VE in the <1 year olds (84.4% VE; 95% CI 23-97%) but negative VE in >1 year olds (-79% VE; 95% CI -556 to 51%), the authors indicated that this could be because of a low sample size in the older group and a change in the predominant rotavirus strains circulating in Colombia during the study to heterotypic non-vaccine strains (185).

Additionally, whilst prior to vaccination the predominant strain type in many high-income countries was G1P (36,124) in lower and middle-income countries there is often greater strain diversity and concurrent circulation of several strains (12,36). It is possible that the frequency of more strains that are heterotypic to vaccine types may contribute to the lower VE in middle-income countries. However, there are likely to be inherent immunological and epidemiological factors at play (202).

Using meta-analysis to review VE against community consultations for AGE is particularly important in high income countries where the majority of the healthcare burden from rotavirus infection is in community healthcare settings. For instance in the UK rotavirus was deemed to be responsible for approximately 800 000 general practice consultations per year prior to vaccine introduction (30). Pooled estimates presented here show considerably lower VE against AGE community consultations compared with RVGE hospitalisations in high income countries. Since only one study is available for middle income countries, evaluation of the effectiveness of vaccination against AGE community consultations in this setting is difficult, particularly because this study had high risk of bias predominantly due to significant differences in age of the vaccinated and unvaccinated cohorts.

Whereas clinical trials have suggested lower efficacy against milder disease (67,203), a single study here reported VE against laboratory confirmed RVGE community consultations on par with VE against RVGE hospitalisations (176,177). Whilst there was no indicator of disease severity in the study, the healthcare setting suggests milder disease. Therefore there is a need for more robustly designed studies in middle-income settings and high-income countries in order to properly assess rotavirus VE against milder disease resulting in community consultations for RVGE.

Studies reviewed here represent countries with a World Bank Country classification of high- or middle-income, and clearly show lower VE in middle-income countries. However, the burden of disease is likely to be greater in middle-income countries representing a greater potential population benefit of vaccination in these settings. At the time of review no studies could be included from low-income settings However, findings from a recent study in Malawi suggest a VE of 64% (95% CI 24–83), similar to that reported in middle-income countries (204). Future reviews will be required to capture studies from these settings.

As these studies were conducted in the "real world" with population level vaccine introduction the VE estimates are likely to include both the direct effect and any herd protective effect of population vaccination. This could be particularly significant in cohort studies with high population vaccine uptake. Indeed only one study attempted to separate the herd protection and direct effect from the overall effect of vaccination, estimating a substantial increase in indirect effect of vaccination as cohort vaccine uptake increased over time (85). More evidence of the indirect effect of vaccination is therefore required through subsequent cohort studies.

We searched three widely used databases—PubMed, Web of Science, and Academic Search Premier —as well as grey literature using a pre-specified, systematic search protocol. We were able to quality assess the studies included using an established critically appraised tool specifically for use with non-randomised studies in meta-analysis, allowing a good understanding of a studies validity importantly with reference to RCT as a gold standard. The majority of studies were assessed as being at low or moderate risk of bias strengthening the meta-analysis for RVGE hospitalisation. However, our assessment of study bias used one specific tool, the NOS, with some author defined criteria. Therefore, it is possible that another bias

assessment tool and criteria would identify a different risk of bias. Furthermore, variations in study outcome definitions and statistical methods could have introduced error into some of our meta-analyses. For instance, heterogeneity was moderate to high in some of the meta-analyses, particularly those that examined community consultations; this could be related to varying definitions of a community consultation.

3.6 Conclusions

This review and meta-analysis has enabled the systematic production of pooled VE estimates for rotavirus vaccination globally from the literature. We conclude that rotavirus vaccines represent a highly effective preventive measure against severe rotavirus disease, with “real world” VE estimates as high as efficacy measures from RCTs. There is sufficient evidence to promote the continued roll out of both rotavirus vaccines in both high- and middle-income settings. The modest benefits from vaccination against community consultations for RVGE represent information which can be used in appropriate cost-effectiveness studies, which may provide better understanding of the value of reducing mild to moderate disease through vaccination.

4 Study protocol and general methods

4.1 Abstract

Introduction: Rotavirus was the most common cause of severe gastroenteritis in infants and young children worldwide. Currently 90 countries include rotavirus vaccine in childhood immunisation programmes, but uptake in Western Europe has been slow. In July 2013, rotavirus vaccine was introduced into the UK's routine childhood immunisation programme. Prior to vaccine introduction in the UK, rotavirus was estimated to result in 750,000 diarrhoea episodes and 80,000 general practice (GP) consultations each year, together with 45% and 20% of hospital admissions and emergency department attendances for acute gastroenteritis, in children under 5 years of age. This chapter describes the protocol for an ecological study that assessed rotavirus vaccine impact in the UK, to inform rotavirus immunisation policy in the UK and in other Western European countries.

Methods and analysis: In Merseyside, UK, we conducted an ecological study using a 'before and after' approach to examine changes in gastroenteritis and rotavirus incidence following the introduction of rotavirus vaccination. Data were collected on mortality, hospital admissions, nosocomial infection, emergency department attendances, GP consultations and community health consultations to capture all healthcare providers in the region. We assessed both the direct and indirect effects of the vaccine on the study population. Comparisons of outcome indicator rates were made in relation to vaccine uptake and socioeconomic status.

Ethics and dissemination: The study was approved by NHS Research Ethics Committee, South Central-Berkshire REC Reference: 14/SC/1140. Study outputs will be disseminated through scientific conferences and peer-reviewed publications.

The study will demonstrate the impact of rotavirus vaccination on the burden of disease from a complete health system perspective.

4.2 Background

In the UK, rotavirus gastroenteritis (RVGE) is seasonal, with most cases occuring between February and April each year. Prior to vaccine introduction rotavirus was estimated to result in 750,000 diarrhoea episodes and 80,000 general practice (GP) consultations each year in the UK (30), together with 45% and 20% of hospital admissions and emergency department (ED) attendances for acute gastroenteritis (AGE), respectively, in children under 5 years of age (29). The economic cost of RVGE to the health service was estimated to be approximately £14 million per year in England and Wales (29). At Alder Hey Children's NHS Foundation Trust, Liverpool, UK, rotavirus was a major cause of community-acquired and healthcare-associated diarrhoea; in a 2-year prospective study among hospitalised children, rotavirus was detected by RT-PCR in 43% of community-acquired and in 31% of healthcare-associated gastroenteritis cases (205). AGE hospital admissions are known to have a positive correlation with socioeconomic deprivation and globally the burden of severe RVGE is much higher in low income countries (159). However, RVGE has not yet been correlated with socioeconomic deprivation in the UK.

In July 2013, the Department of Health introduced a rotavirus vaccine into the UK's routine childhood immunisation programme (158,206). The live-attenuated, two dose oral monovalent vaccine (RV1, Rotarix®, GlaxoSmithKline Biologicals, Belgium) is administered at 2 and 3 months of age. At present more than 90 countries include a rotavirus vaccine in their childhood immunisation programmes (73). Based on the uptake of other routine childhood vaccinations in the UK, coverage of over 90% would be expected for rotavirus vaccine (207); initial figures

for England indicate 93% uptake for first dose and 88% for the second dose of rotavirus vaccine (208).

Clinical trials in middle-income and high-income countries demonstrated high (>85%) efficacy against severe RVGE (61). The introduction of rotavirus vaccines in the immunisation programmes of these countries has demonstrated direct benefits on a par with those observed in clinical trials, with significant reductions in diarrhoea hospitalisations (209). An unanticipated but beneficial consequence of rotavirus vaccination has been the reduction of rotavirus disease in unvaccinated individuals ('herd' protection), likely due to reduced virus transmission. Such 'indirect benefits' include reduced disease in non-vaccinated older children and adults who were not thought to sustain a significant burden of rotavirus disease (134). In the UK, the burden of RVGE in older children and adults is difficult to estimate but admissions for AGE are 2 per 1,000 population in 5–14-year-olds and 7 per 1,000 in those 15+ years of age (210). Hence monitoring changes in AGE incidence in non-vaccinated older children and adults is critical to assess indirect impact.

Ecological rotavirus vaccine effectiveness studies have primarily focused on mortality, hospitalisations and laboratory detections as a measure of burden (103,136,145,187,192,211–213). Severe cases of rotavirus infection will often end up in hospital and receive full diagnostic evaluation. However, many cases of rotavirus infection, particularly in older children and adults, will not attend hospital but will be seen by primary and community healthcare providers. Therefore, in order to better understand the burden of RVGE and AGE on all ages and the impact of routine immunisation on the health system, it is crucial to examine routine data sources for all health service providers in a defined study area. Taking advantage of a range of regional healthcare facilities in Merseyside, UK, we conducted an

ecological study which uses a ‘before and after’ approach allowing comprehensive evaluation of the direct and indirect vaccine impact following the introduction of the monovalent rotavirus vaccine into the UK's routine childhood immunisation programme. We investigated the relationship between socioeconomic deprivation, and vaccine uptake and disease burden. These data will provide evidence to support future rotavirus vaccination in the UK and will inform rotavirus immunisation policy in other Western European countries (158).

4.3 Methods

Each results chapter in this thesis includes a detailed methods section. Presented below is a generalised summary of the methods used, adapted from the published study protocol (214).

4.3.1 Study aim

Routine data sources were used to estimate the direct and indirect effects of monovalent rotavirus vaccination on gastroenteritis indicators in the population of Merseyside, UK, and their relationship to vaccine coverage and sociodemographic indicators. We also hoped to identify the key areas that require extended and improved data collection tools to maximise the usefulness of this surveillance approach. The main outcome measures are:

- Laboratory detections of rotavirus in faecal samples;
- Admissions to hospital for RVGE or AGE;
- Attendances to EDs for AGE;
- Number of nosocomially acquired cases of RVGE;
- GP and community consultations for diarrhoea and AGE;
- Routine rotavirus vaccine coverage mapping by small area geography;

- Relative contribution of direct (those vaccinated) and indirect (not vaccinated) effects to overall vaccine benefit in health system usage for both RVGE and AGE;
- Relationship between socioeconomic deprivation, vaccine uptake and RVGE / AGE incidence.

4.3.2 Study setting and location

The study was conducted in the large metropolitan area of Merseyside in North West England which contains five local authorities (Knowsley, Liverpool, Sefton, St Helens and Wirral). Merseyside has a population of ~1.4 million people, with approximately 80,000 of its population under 5 years of age. Socioeconomic deprivation within Merseyside is variable but over 60% of its population live in a more socioeconomically deprived area than the England average (Figure 4-1) (215). Vaccination uptake for most routine childhood vaccinations is also variable in small areas, but overall Merseyside has uptake above the national average for England (207). Healthcare for the population is self-contained with the region and including a specialist paediatric hospital.

4.3.3 Study overview and choice of study designs

The study employed an ecological design, utilising routine health surveillance data before and after rotavirus vaccine introduction. The evaluation incorporates interrupted time-series analyses of outcome indicators across the study population. Comparisons of outcome indicator rates were made between communities with high vaccine uptake and those with lower vaccine uptake and the relationship with socioeconomic deprivation. The ecological study approach allows population-based rates of outcomes to be compared in space and time using vaccine uptake and community-level socioeconomic deprivation as covariates.

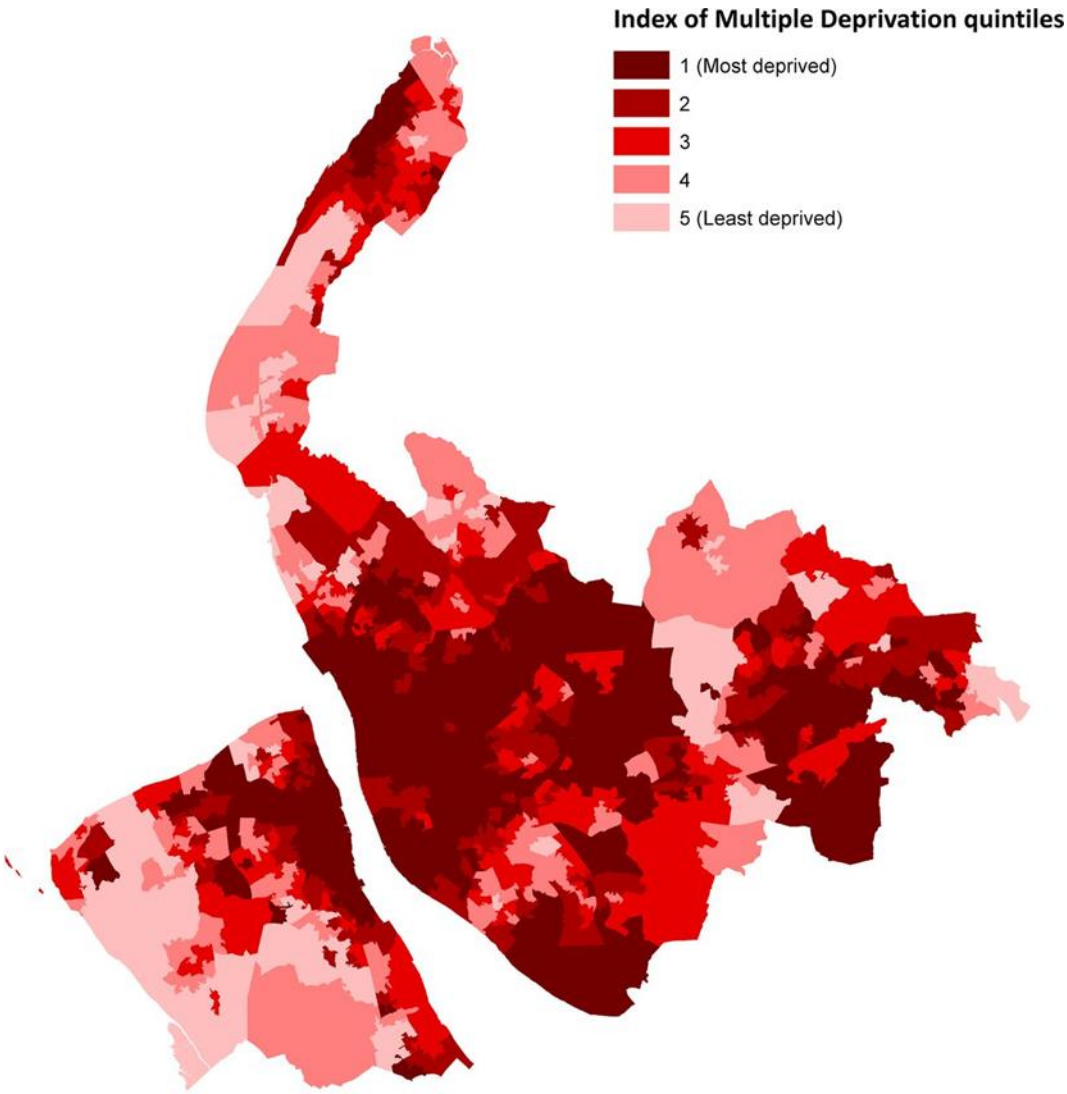

Figure 4-1 Socioeconomic deprivation in Merseyside

[Produced using the English Indices of Deprivation 2010, national quintiles for the Index of Multiple Deprivation (210).]

4.3.4 Study data

The National Health Service (NHS) in England and other government service agencies collect a range of administrative and healthcare data which is held at both local service level and centrally. Figure 4-2 outlines the data sources that were used for the evaluation and Table 4-1 shows the case definitions.

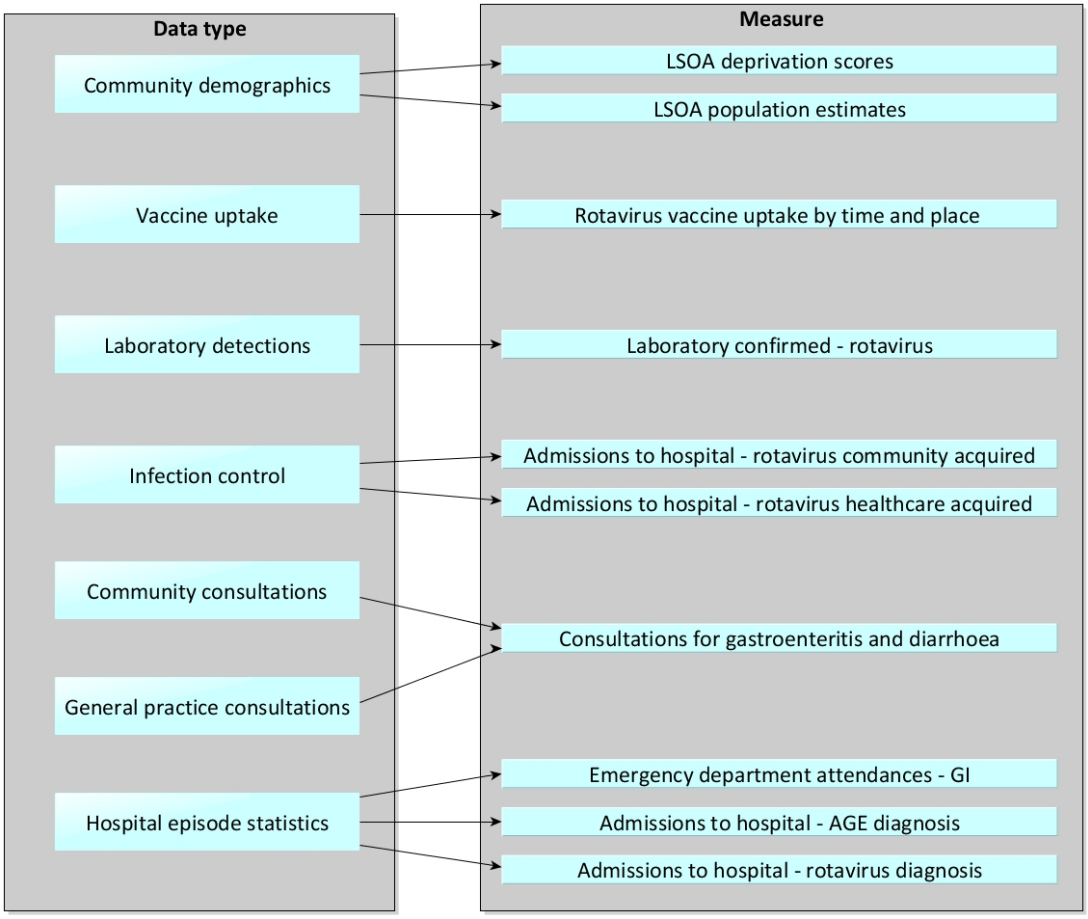

Figure 4-2 Schematic of study data sources and outcome measures [LSOA, Lower Super Output Area]

Hospital admission and ED attendance data were obtained from hospital episode statistics (HES) (210), which record all inpatient admissions in NHS hospitals in England. The study measured hospitalisations and ED attendances for residents of Merseyside receiving care in hospitals throughout England.

GP consultation data for diarrhoea or gastroenteritis was obtained from Clinical Commissioning Groups covering Merseyside. Community consultations for diarrhoea and gastroenteritis at 'Walk-in Centres' were sourced from NHS Community Health Trusts. Walk-in Centres are primarily nurse-led primary care facilities for illness and injuries without need for prior appointment.

RVGE at Alder Hey Children's NHS Foundation Trust (Alder Hey) in Liverpool is classified as community acquired or nosocomial. Alder Hey's footprint covers the majority of Merseyside's children, so these data enabled the evaluation of the effect of rotavirus vaccination on nosocomial rotavirus infection in children across Merseyside.

Each dataset covered at least 3 years either side of vaccine introduction. All data were pseudoanonymised to allow distinction of records but no linking of datasets or identification of individuals was undertaken. Data were either geocoded from postcode to small statistical geographical community units termed Lower Super Output Areas (LSOAs) or sourced with this geography. In each LSOAs there is approximately 1,500 persons, with denominator populations derived from the Office for National Statistics (ONS) mid-year population estimates by LSOA (216). Indicators of socioeconomic deprivation at LSOA level were measured using the English Indices of Deprivation. The UK Department for Communities and Local Government produce the English Indices of Deprivation using census and other local administrative data (215). Rotavirus vaccination uptake data were sourced from the Child Health Information System (CHIS) which is held by community NHS health Trusts in Merseyside. Records of doses of vaccinations given as part of the UK childhood vaccine schedule are recorded in CHIS for each child.

Table 4-1 Case definitions by health dataset

Dataset	Case definition
Nosocomial and community acquired	Nosocomial – Laboratory confirmed rotavirus case. Gastroenteritis symptoms beginning more than 48 hours after admission Community acquired – Laboratory confirmed rotavirus case. Gastroenteritis symptoms starting within 48 hours of admission
Hospital admissions	Rotavirus case definition - Inpatient finished consultant episodes (FCE) with a primary or subsidiary diagnosis International Classification of Disease version-10 (ICD-10) diagnosis code of A08.0 AGE case definition – inpatient FCE with a primary or subsidiary diagnosis ICD10 code of intestinal infectious disease (A00 - A09) and non-infectious gastroenteritis (K52.9).
Emergency attendances	Attendance with a primary or secondary diagnosis HES Accident and Emergency diagnosis code of 26 Gastrointestinal conditions (those subsequently admitted excluded to prevent duplication in hospital admissions)
GP Consultations	GP consultations with a Read Code of (Read Codes in parenthesis): gastroenteritis—presumed infectious origin (A0812), diarrhoea of presumed infectious origin (A083); infantile viral gastroenteritis (A07y1); infectious gastroenteritis (A0803); enteritis due to rotavirus (A0762); infectious diarrhoea (A082); diarrhoea and vomiting (19G); diarrhoea symptom NOS (19F6); and diarrhoea (19F2). Infectious gastroenteritis will be used as the primary case definition but diarrhoea / vomiting will also be included for a secondary indicator of burden.
Community consultations (Walk-in-Centres)	There is no consistent approach to diagnosis coding across providers. Read Codes (see above codes), Accident and Emergency diagnosis codes (see above codes), and free-text are used across Merseyside.
Laboratory detections	Detection of rotavirus in a faecal specimen by a standard enzyme immunoassay.

4.3.5 Quality control

Data sources such as HES and laboratory detections will be influenced by testing practices; for instance, testing of some organisms is more likely to occur at certain times of the year. In the hospital admission dataset, it is possible that some cases of RVGE will not be coded as rotaviral enteritis (ICD10: A08.0) and may be classified as other unspecified either due to an absence of laboratory confirmation or

misclassification / miscoding. In order to attempt to quantify this information bias, the investigator team performed quality control on hospital admissions and laboratory detections at the lead NHS Trust hospital site (Alder Hey). Using a sample of cases from at least 3 years, those cases with a laboratory confirmation were checked against clinical records and clinic coding and those coded as ICD10 A08.0 rotaviral enteritis were cross-matched against laboratory detections.

4.3.6 Ethical considerations

The study has been approved by NHS Research Ethics Committee, South Central-Berkshire REC Reference: 14/SC/1140. Data sharing agreement were obtained between PHE, participating NHS Trusts and the University of Liverpool. Research governance approval and data sharing agreements were sought from all participating NHS Trusts, Clinical Commissioning Groups and GP practices.

4.3.7 Data analysis

Changes in trends of primary care consultations, community consultations, ED attendances, hospitalisations and rotavirus detections were explored using interrupted time-series analysis. Population-based rates for a minimum of a 3-year period prior to vaccination and year on year after vaccination (for 3 years) were compared. For the regression analyses, Poisson or negative binomial regression were used. We first computed monthly population-based rates that were expected to occur in the absence of a rotavirus vaccination programme by fitting the model to pre-vaccine data. We then adjust for secular and seasonal trends. The models were used to estimate ‘expected’ population-based rates after vaccination and compared with ‘observed’ population-based rates. Rate ratios were calculated to assess the magnitude of decline in rates. Potential data biases were controlled for by the access and analysis of multiple health data sources.

4.3.8 Power calculation

Based on hospital admissions for RVGE in 2012 obtained from HES data, the estimated rate of RVGE hospitalisation is approximately 1 per 1,000 children under age 5 years in England (210). Assuming high vaccine uptake rates (i.e. 95%), similar to uptake of other routine childhood vaccines in Merseyside, we used a one sample comparison of proportions for a two-sided test to calculate the power estimates (Table 4-2). Studies from other high income countries on the population effects of rotavirus vaccination have shown reductions in hospital admissions of over 50% in children under 5 years of age (140). Assuming a similar reduction in Merseyside, this study has over 90% power to detect a significant change in RVGE hospital admissions.

Table 4-2 Predicted power of study for main outcome (hospitalisation rate) in Merseyside and selected sub-districts

Area	Estimated population (children <5 years of age)	Assumed reduction in rotavirus hospitalisation rate				
		25%	30%	40%	50%	75%
Liverpool	27000	0.22	0.31	0.56	0.82	1
Liverpool and Sefton	41000	0.34	0.48	0.78	0.96	1
Liverpool, Sefton and Knowsley	50000	0.41	0.58	0.87	0.99	1
Merseyside	80000	0.63	0.8	0.98	1	1

The study is also powered for detecting an indirect effect in adults. Using an AGE hospital admission rate of 7 per 1,000 population aged 15+ years (210), we would expect power to be at least 0.97 for Merseyside at assumed hospitalisation rate reductions post vaccination of 5%, 8% and 10%. Additionally, for GP consultations for AGE in children under 5, a power of 0.89 and 1 can be achieved, for assumed

consultation rate reductions post vaccination of 5% and 10% respectively. No formal power calculations have been undertaken for other end points under study.

4.3.9 Project governance

A stakeholder group within Merseyside was established to enable effective achievement of the project objectives and ownership by the professional community. The stakeholder group includes representatives from: Liverpool Health Partners (217); Liverpool Community Health NHS Trust (218); NHS England Merseyside Area Team Screening and Immunisation Team (207); Alder Hey Children's NHS Foundation Trust (219); NHS CCGs in Merseyside and Public Health England-Liverpool (220).

4.4 Discussion

This study will enable demonstration of a complete health system perspective of the impact of rotavirus vaccination on the burden of disease in Merseyside, UK. It aims to study both direct and indirect effects of routine rotavirus vaccination. The study will also enable data on vaccine efficacy to infer the relative contribution of RVGE to AGE primary care, and emergency care consultations. Furthermore, as data will be linked to specific geographical units, for which information on socioeconomic deprivation and vaccine uptake is available, the association of these with disease burden can be explored. Quality control procedures contained within the study will provide a means of adjusting analysis for information bias and also enable identification of the key data collection issues that require improvement to maximise the usefulness of this surveillance approach. It is also hoped that this study will provide a learning resource and template for similar ecological approaches to examine effectiveness of other vaccines in the UK in the future.

4.4.1 Strengths

A whole health system approach in a geographically defined area provides a number of strengths. Using datasets from a range of healthcare providers within a health economy will allow us to examine the relative impact of vaccination on the various health providers rather than the individual. The use of multiple data sources to measure independent indicators of vaccination effect also provides robustness, enabling easier identification of outliers from overall trends.

Since there is annual variability in the number of rotavirus cases, it is imperative to conduct surveillance of rotavirus incidence over a number of years pre-vaccine and post-vaccine introduction. This study will provide a mechanism to do this as it will cover three rotavirus seasons post-vaccine introduction. Thus, cofounding caused by yearly variance in rotavirus numbers will be minimised.

There are limited published data describing the indirect effect of routine vaccination on unvaccinated older children and adults and the majority of studies have focused on hospital admissions. As this study will collect data for all ages and cover RVGE and AGE incidence 3 years post-vaccination, it will provide sufficient data for measurement of the indirect effect on hospital admissions. As well as examining indirect effects in EDs and community settings. This is particularly important as it is perhaps more likely that moderate / severe RVGE in unvaccinated older children and adults will be treated at EDs and through community consultations.

Another potential strength of the study is the ability to conduct analysis at small community (LSOA) level. This will enable small area sociodemographic information such as socioeconomic deprivation to be included in the analyses as a covariate at the lowest possible unit of analysis other than the individual. Thus, allowing the

exploration of the association between socioeconomic deprivation, burden of RVGE / AGE and vaccine uptake while limiting the ecological fallacy of analysis.

As many of the data sources included in this study do not include specific RVGE classification, AGE is used as an outcome measure for most datasets. Laboratory detection data which are organism specific has allowed the adjustment of these measures based on the seasonal contribution of organisms other than rotavirus such as norovirus. For example, RVGE seasonality is fairly constant but that of norovirus tends to vary over the winter and spring months in the UK. These AGE indicators were adjusted for seasonality (Figure 4-3) to give a better proxy of the contribution of rotavirus to overall AGE causes and the relative impact of rotavirus vaccination (221).

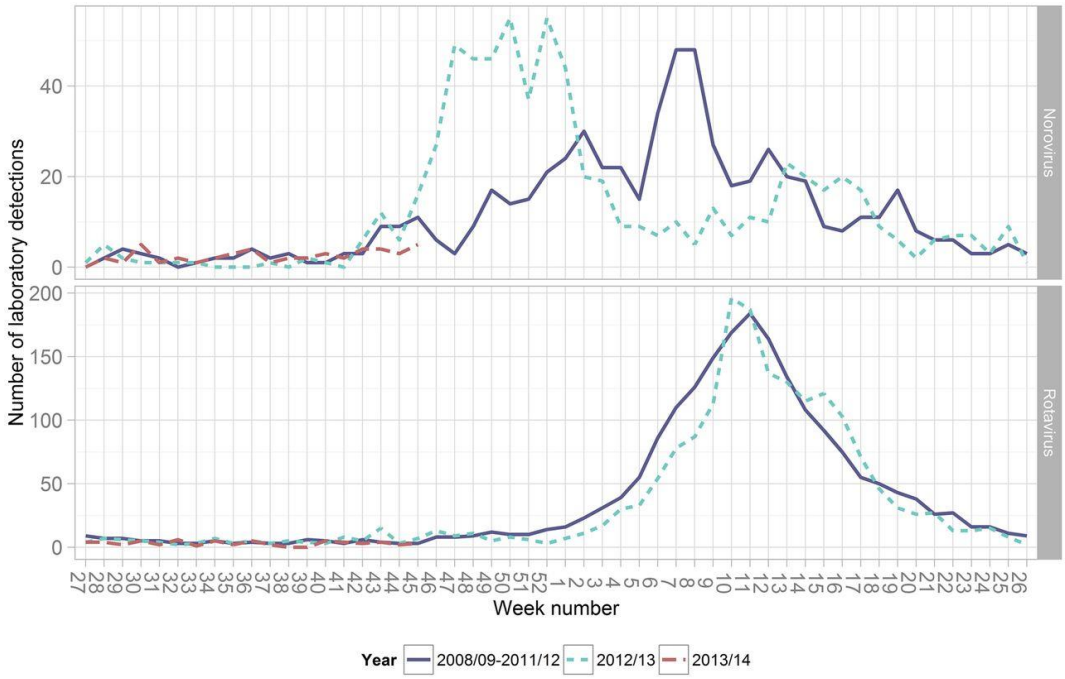

Figure 4-3 Laboratory detections of norovirus (top) and rotavirus (bottom) in the North West, England, 2009/10–2013–14 [Laboratory reports are from LabBase2 system at Public Health England, (221)]

4.4.2 Limitations

The gold standard for measurement of vaccine efficacy is the randomised controlled trial. However, this ecological study will investigate the impact of vaccination on population disease burden within a health system; therefore, an ecological study is appropriate. Conversely it is recognised that an ecological approach cannot show individual-level effects of vaccine and can only infer the impact of the vaccine at the population level without causation. Additionally, a key focus of this study is to quantify variation in the outcomes measured according to vaccine uptake levels and socioeconomic deprivation. Confounding may be an issue since cases living in areas with low vaccine uptake or high socioeconomic deprivation may also have other characteristics that will affect the risk of RVGE or AGE.

For measures of AGE activity in community settings (e.g., GP and Walk-in Centre), syndromic indicators that are non-specific to rotavirus, for example, diarrhoea, vomiting, were used. An inherent issue is that the ability to detect effect on these is likely to be limited to large effects rather than small variations.

A further limitation of the study is that investigators will not collect data directly as all data are secondary, with consequent risk of bias. There is potential for clinical coding to lead to misclassification of disease, and this misclassification may vary by different data sources. We will describe these biases through quality control and subsequently adjust for them at the analysis stage. The use of multiple datasets for outcome indicators limits these issues by improving robustness.

It is likely that there have been changes in data collection methods over the study period, for example, changes to the assay used for rotavirus laboratory testing, leading to testing bias. One way to adjust for this in the analysis is to smooth

fluctuations caused by changes in testing methods. Contact with rotavirus testing laboratories and NHS Trusts, has allowed changes to be described and where possible assist appropriate analytical adjustments. It is also feasible that the introduction of vaccination may also trigger changes in clinician requests for rotavirus and other AGE diagnostic testing, particularly in the vaccination age group. Any possible testing bias was assessed at the lead NHS Trust via comparisons with pre-vaccine testing probabilities.

The study does not include any economic component. However, previous studies have reported the likely cost-effectiveness of rotavirus vaccination for the population under 5 years of age (222). This study will provide the results and data necessary for economic evaluation based on the direct and indirect impact of rotavirus vaccination.

5 Early impact of rotavirus vaccination in a large paediatric hospital in the UK

5.1 Abstract

The impact of routine rotavirus vaccination on community-acquired (CA)- and healthcare-associated (HA)-rotavirus gastroenteritis (RVGE) at a large paediatric hospital, UK, was investigated over a 13 year period. A total of 1644 hospitalised children aged 0-15 years tested positive for rotavirus between July 2002 and June 2015. Interrupted time-series analysis demonstrated that post-vaccine introduction (July 2013-June 2015), CA- and HA-RVGE hospitalisations were 83% (95% CI 72-90%) and 83% (95% CI 66-92%) lower than expected, respectively. Rotavirus vaccination has rapidly reduced the hospital rotavirus disease burden among both CA- and HA-RVGE cases.

5.2 Background

Prior to rotavirus vaccine introduction rotavirus was an important cause of healthcare-associated (HA) gastroenteritis; among children at a large paediatric hospital, UK, rotavirus was detected by reverse transcription-polymerase chain reaction (RT-PCR) in 43% of community-acquired (CA) and in 31% of HA-gastroenteritis cases (205). Since the UK introduced the live-attenuated, two dose oral monovalent rotavirus vaccine (RV1, Rotarix®, GlaxoSmithKline Biologicals SA, Belgium) with doses given at two and three months of age (158). Early impact studies in the UK suggested a large reduction (77%) in laboratory-confirmed rotavirus infections in vaccine age-eligible infants (223). However, no impact on HA-infection has yet been described. Understanding the impact of rotavirus vaccination on both CA- and HA-RVGE cases may have implications for both

hospital infection control and bed management policies, and will help inform the evidence base for continued immunisation in the UK.

This retrospective investigation aimed to quantify the impact of rotavirus vaccination on HA- and CA-RVGE cases at the same children's hospital as our prospectively conducted study from the pre-vaccine period (205).

5.3 Methods

5.3.1 Study setting

The study was conducted at Alder Hey Children's NHS Foundation Trust, Liverpool, UK (Alder Hey). Alder Hey provides primary, secondary, and tertiary care facilities for >200,000 children each year and has approximately 240 inpatient beds. General medicine, general surgery, and a range of specialist services including critical care, oncology, cardiac, and neurosurgery are provided; there is also a large emergency department.

5.3.2 Case definition

Children aged between 0 and 15 years who were admitted with RVGE between July 2002 and June 2015, or those in whom RVGE developed after hospitalisation, were eligible for inclusion. Testing for rotavirus was conducted on clinician request throughout the study period with no age restriction. RVGE was defined as rotavirus antigen detected by immunochromatographic test or by enzyme immunoassay in a faecal specimen of a child with acute gastroenteritis. RVGE was considered HA if gastroenteritis developed ≥48 hours after admission and there was no record of diarrhoea or vomiting on admission. Clinical and anonymised demographic data were collected for each participant, and included information on specimen date, admission date, age and symptoms on admission. The pre-vaccine period was

defined as July 2002 to June 2013 and the vaccine period was defined as July 2013 to June 2015.

5.3.3 Statistical analysis

To assess the impact of rotavirus vaccination on hospitalisations for CA- and HA-RVGE, an interrupted time-series methodology was used. Firstly, monthly expected incidence of rotavirus hospitalisations was estimated by fitting a negative binomial regression model to pre-vaccine monthly incidence data, offset for total monthly admissions and adjusting for seasonality and secular trends using calendar month and rotavirus year (July to June), respectively (214). This model was used to predict the counter-factual numbers of RVGE hospitalisations (in the absence of vaccination) for the vaccine period, where the impact of vaccination is expressed by the difference between the counter-factual expectation and observed number of hospitalisations. To quantify change in the number of RVGE hospitalisations by the introduction of the vaccine, a second model included a derived binary indicator variable for the post-vaccine period, enabling the computation of risk ratios (RR) and associated 95% confidence interval (CI). This second model offset for total monthly admissions and adjusted for month and rotavirus year. Percentage change in incidence was calculated as $100 \times (1 - RR)$. The analysis was undertaken separately for CA- and HA-RVGE hospitalisations. To investigate the impact of routine vaccination on different age groups the analysis stratified overall RVGE hospitalisations by age group (<2 years old and 2-4 years).

Demographic and clinical characteristics were compared between RVGE cases from the pre and post-vaccine periods and between CA- and HA-RVGE cases. For continuous variables we used a t-test or Wilcoxon rank-sum test if not normally

distributed and χ^2 or Fisher's exact test for categorical variables. All data handling and statistical analyses were performed using R Version 3.1.2 (224).

5.3.4 Ethical approval

Ethical approval was provided by NHS Research Ethics Committee, South Central-Berkshire (Reference: 14/SC/1140).

5.4 Results

A total of 1644 hospitalised cases of RVGE were documented between July 2002 and June 2015. CA-cases accounted for 74.2% (n=1220) of all RVGE cases, 25.4% (n=418) cases were HA-RVGE and 0.4% (n=6) did not meet the case definition for either HA or CA. In the pre-vaccine period there was a mean of 145 RVGE hospitalisations per year (range: 109-191), comprising 108 (83-150) CA- and 37 (18-58) HA cases (Table 5-1). In the first post-vaccine year (July 2013-June 2014) there were a total of 22 RVGE cases and in the subsequent year (July 2014 – June 2015) there were 30 RVGE cases. In the pre-vaccine period 25% (range: 15-35%) of RVGE cases were classified as HA compared with 29% (18% in 2013/14; 37% in 2014/15) in the vaccine period (p=0.6).

There was an estimated 82% reduction in RVGE hospitalisations (95% CI 70-89%) in the vaccine period, compared with what would have been expected in the absence of vaccination (Table 5-1; Figure 5-1). Most of the decline occurred in vaccine age-eligible children <2 years old (84%: 95% CI 74-90%). A reduction of 69% (95% CI 38-86%) was observed in children age 2-4 years who were too old to have been vaccinated. There was an insufficient number of RVGE hospitalisations in children aged over 5 years in the pre-vaccine era (mean per year=12; range 6-20) to enable fitting of the regression model (Table 5-1). The magnitude of reduction in

hospitalisations in the vaccine period was similar in both CA-RVGE (83%: 95% CI 72-90%) and HA-RVGE (83%: 95% CI 66-92%) cases (Table 5-1; Figure 5-1).

The median age of pre-vaccine CA-RVGE cases (12 months, Interquartile Range [IQR] 7-23), was lower than the age of CA-RVGE cases from the vaccine period (23 months, IQR 14-26; p<0.001). The median age of -HA-RVGE cases that occurred in the pre-vaccine period (9 months, IQR 4-22), was non-significantly higher than that of HA-RVGE cases in the vaccine period (5 months, IQR 4-14; p=0.131). The median age of CA-RVGE cases in the pre-vaccine period was significantly higher than that of HA-RVGE cases (p<0.001), with this age difference even greater in the vaccine period (p<0.001).

Table 5-1 RVGE hospitalisations at Alder Hey among children 0-15 years of age, pre- and post-rotavirus vaccine introduction

	Yearly mean No. of hospitalisations (range) pre-vaccine introduction, July 2002-June 2013*	No. of hospitalisations post-vaccine introduction, July 2013-June 2015		Risk Ratio (95% CI)	Percent decline in hospitalisations (95% CI)†	p-value
Age		Year 1	Year 2			
0-15 years	145 (109-191)	22	30	0.18 (0.11-0.30)	82 (70-89)	<0.001
<2 years	111 (88-145)	17	16	0.16 (0.10-0.26)	84 (74-90)	<0.001
2-4 years	22 (15-32)	2	13	0.31 (0.14-0.62)	69 (38-86)	0.017
5-15 years	12 (6-20)	2	1	-	-	-
CA-RVGE	108 (83-150)	18	19	0.17 (0.10-0.28)	83 (72-90)	<0.001
HA-RVGE	37 (18-58)	4	11	0.17 (0.08-0.34)	83 (66-92)	<0.001

*yearly means are based on a rotavirus year running July to June

†Calculated as 1-risk ratio. Risk ratio was calculated using a negative binomial model adjusting for calendar month and rotavirus year.

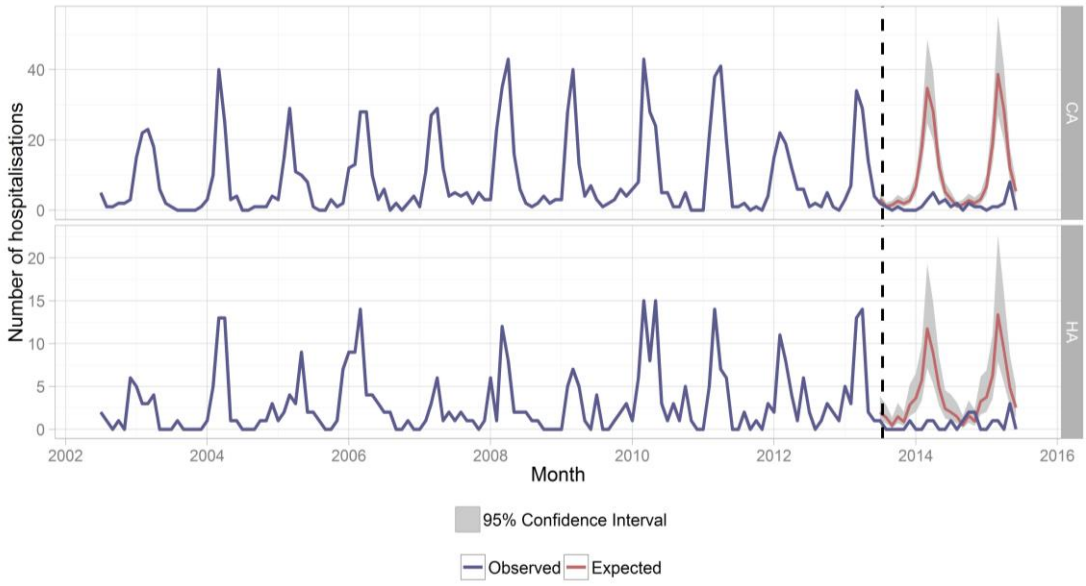

Figure 5-1 CA- and HA-RVGE hospitalisations at Alder Hey, July 2002 to June 2015 [The blue line is the number of observed RVGE hospitalisations; the red line is the RVGE hospitalisations expected and the grey shading the 95% confidence intervals for the expected. The black hashed line represents the introduction of rotavirus vaccine in the UK in July 2013.]

5.5 Discussion

Since the introduction in 2013 of routine rotavirus vaccination in the UK there has been a significant decline in hospitalisations for RVGE in this large paediatric hospital. The magnitude of reduction was similar for both CA- and HA-RVGE cases. Age stratified analysis provided further evidence that the reduction in hospitalisations is highly likely to be due to the impact of vaccination as the largest reduction was observed in vaccine eligible infants <2 years of age. Furthermore, as shown in other settings, there was an increase in age of RVGE cases post-vaccine introduction (204,223). The observed reduction in vaccine ineligible older age groups (2-4 years) is similar to that observed through national laboratory surveillance and may be indicative of an indirect effect of vaccination (223).

We established that HA-RVGE cases were significantly younger than CA-RVGE cases. Furthermore, an increase in age in the vaccine period was observed among CA-RVGE cases but this was not observed among HA-RVGE cases. Similar age

profiles were also observed at a paediatric hospital in Greece following vaccine introduction (225). These data suggest that hospitalised infants remain at risk of developing HA-RVGE even among highly vaccinated populations, possibly through direct or indirect exposure to rotavirus from older children and adults.

Our study relied upon rotavirus antigen testing in stools, which is known to be a better predictor of symptomatic rotavirus disease than PCR-based methods; interpretation of a positive PCR result is rendered difficult because of the high frequency of asymptomatic rotavirus shedding in young children, necessitating the development of a real-time PCR cut-off to define symptomatic infection (21). Therefore, it is likely that the cases in this study represent clinical disease. Although rotavirus vaccination cannot be definitively established as the cause of the observed reduction in RVGE hospitalisations due to the ecological nature of this study, there are additional factors which suggest vaccine impact. The reduction in CA- and HA-RVGE cases in the vaccine period has not been mirrored by a similar decline in respiratory syncytial virus (RSV) infection, another viral pathogen that predominately affects young children in winter; indeed, the incidence of HA-RSV infection has remained stable whilst RSV infection has increased in the community (data not shown). There were also no major changes in hospital infection prevention and control policies during the period of study. Finally, our study examined two post-vaccine seasons and took into account long-term seasonal and annual trends.

This study has demonstrated that since the introduction of routine rotavirus vaccination in the UK, in addition to a marked decline of CA-RVGE cases, there has been a similar fall in HA-RVGE hospitalisations. The reduction in RVGE cases is expected to save bed days and reduce the burden on infection control teams with potential for both clinical and economic benefit.

6 Rotavirus vaccine impact and socioeconomic deprivation: an interrupted time-series analysis of gastrointestinal disease outcomes across primary and secondary care in the UK

6.1 Abstract

Background: Rotavirus causes severe gastroenteritis in infants and young children worldwide. The UK introduced childhood rotavirus vaccination in July 2013. We evaluated vaccine impact across a health system in relation to socioeconomic deprivation.

Methods: We used interrupted time-series analyses to assess changes in monthly healthcare attendances in Merseyside, UK for all ages, from July 2013 to June 2016, compared to predicted counterfactual attendances without vaccination spanning 3-11 years pre-vaccine. Outcome measures included laboratory confirmed rotavirus gastroenteritis (RVGE) hospitalisations; acute gastroenteritis (AGE) hospitalisations; emergency department (ED) attendances for gastrointestinal conditions; and consultations for infectious gastroenteritis at community walk-in-centres (WIC) and general practices (GP). All analyses were stratified by age, hospitalisations were additionally stratified by vaccine uptake and small area-level socioeconomic deprivation.

Results: Uptake of first and second dose of rotavirus vaccine was 91.4% (29,108/31,836) and 86.7% (27,594/31,836), respectively. Among children aged <5 years, the incidence of gastrointestinal disease decreased across all outcomes post-vaccine introduction: 80% (95% confidence interval [95% CI] 70-87%; p<0.001) for RVGE hospitalisation; 44% (95% CI 35-53%; p<0.001) for AGE hospitalisations;

23% (95% CI 11-33%; p<0.001) for ED; 32% (95% CI 7-50%; p=0.02) for WIC; and 13% (95% CI -3-26%; p=0.10) for GP. Impact was greatest during the rotavirus-season and for vaccine eligible age groups. In adults aged 65+ years, AGE hospitalisations fell by 25% (95% CI 19-30%; p<0.001).

The pre-vaccine risk of AGE hospitalisation was highest in the most socioeconomically deprived communities (adjusted incident rate ratio 1.57; 95% CI 1.51-1.64; p<0.001), as was the risk of non-vaccination (adjusted risk ratio 1.54; 95% CI 1.34-1.75; p<0.001). The rate of AGE hospitalisations averted per 1,000 first doses of vaccine was higher among infants in the most deprived communities compared to the least deprived in 2014/15 (28; 95% CI 25-31 vs 15; 95% CI 12-17) and in 2015/16 (26; 95% CI 23-30 vs 13; 95% CI 11-16).

Discussion: Following rotavirus vaccine introduction gastrointestinal disease reduced across the healthcare system. Vaccine impact was greatest among the most deprived populations, despite lower vaccine uptake. Prioritising vaccine uptake in socioeconomically deprived communities should give the greatest health benefit in terms of population disease burden.

6.2 Background

The monovalent rotavirus vaccine (Rotarix®) was introduced into the UK childhood immunisation schedule in July 2013, with two doses delivered at 8 and 12 weeks of age (158). Vaccine uptake in England increased rapidly, reaching over 91% for 1 dose by February 2014 and over 94% by mid-2016 (226). To date, studies in the UK have separately, and for varied populations and time periods, analysed vaccine impact on rotavirus laboratory detections (77% reduction in infants) (223), RVGE hospitalisations (>80% reduction in infants) (227), all cause AGE hospitalisations

(26% in infants),(223) and GP attendances for diarrhoea related illness (20-30% in under 5 year olds) (228).

This study aimed to assess the effect of rotavirus vaccination on multiple levels of the UK healthcare system simultaneously, by examining the trends in hospitalisations, ED attendances, community health consultations and GP consultations for outcomes of gastroenteritis, diarrhoea and rotavirus gastroenteritis (RVGE) in a defined population before and after vaccine introduction. This approach will for the first time provide estimates of rotavirus vaccine impact in a "total health economy". Secondly, within the UK, children under five years of age are over represented in the most socioeconomically deprived populations (229,230), and experience significantly higher incidence of all-cause AGE hospitalisations than more affluent populations (159). It is known that in the UK, uptake of routine childhood vaccines (e.g. vaccines for measles, mumps and rubella, human papillomavirus, influenza) is lower in socioeconomically deprived populations (160,161,163). Thus we examined the uptake and impact of rotavirus vaccination in Merseyside, an area with wide variation in socioeconomic deprivation, in order to assess whether vaccine uptake and impact is equitable.

6.3 Methods

6.3.1 Study setting

The study population was the metropolitan area of Merseyside, England with an estimated resident population of 1.4 million and an annual birth cohort of approximately 16 000. In 2016, 80,000 of the population were under 5 years of age (230). Merseyside contains five local authorities (Knowsley, Liverpool, Sefton, St Helens and Wirral), containing multiple National Health Service (NHS) trusts / organisations. Healthcare for the population is provided in the community by GP

practices and walk-in centres (WICs) offering both primary and urgent care; there are five hospitals with emergency and secondary care facilities including a large paediatric hospital (Alder Hey Children's NHS Foundation Trust). Further description of the organisations and facilities has been previously described (214).

6.3.2 Data sources and case definitions for outcome measures

Data sources and full case definitions have been previously published (214). Table 6-1 summarises these details, and amends any discrepancies. Notably, data on GP consultations were obtained through the NHS clinical commissioning groups (CCGs). Coding for non-infectious gastroenteritis (ICD10 K52.9) was included in the all-cause AGE hospitalisation outcome measure, since unspecified gastroenteritis was classified under this code until April 2012 (231).

6.3.3 Area of residence and socioeconomic deprivation

In each of the health datasets accessed, an indicator for neighbourhood area of residence (Lower Super Output Area [LSOA]) was included. English LSOAs are small statistical boundaries defined following the 2001 and 2011 censuses and consist of approximately 1,500 people. A standardised measure of socioeconomic deprivation was assigned to each participant, using the LSOA of their residence and the English indices of deprivation 2015, the Index of Multiple Deprivation (IMD) (229).

Table 6-1. Details of each outcome measure and data source

Data source	Population	Outcome	Denominator / offset	Age in months (m) or years (y)	Time period
Alder Hey Children's NHS Foundation Trust - laboratory reports	Hospitalisations. Alder Hey's footprint covers the majority of Merseyside's children	Laboratory confirmed rotavirus gastroenteritis. Rotavirus antigen detected by immunochromatography test or by enzyme immunoassay in a faecal specimen of a child with acute gastroenteritis	Total hospitalisations per month by age group	0-14y: <12m; 12-23m; 24-59m; 5-14y	July 2002 to June 2016
Hospital episode statistics - Admitted Patient Care	Merseyside residents attending any hospital in the UK	Hospitalisation for all cause acute gastroenteritis. Identified by ICD10 codes: A00-A09) or as non-infectious gastroenteritis (K52.9), in any diagnosis field	Yearly estimated age specific population of Merseyside. Source: Office for National Statistics; accessed through Public Health England [17]	All ages: <12m; 12-23m; 24-59m; 5-14y; 15-64y; 65+	July 2000 to June 2016
Hospital episode statistics – Accident and Emergency	Merseyside residents attending three major emergency departments in Merseyside	Emergency department attendance for gastrointestinal conditions (AE diagnosis code 26); excluding subsequent admissions. Missing diagnosis data was imputed for one emergency department between November 2010 and March 2011	Total emergency department attendances (excluding subsequent admissions) per month by age group	All ages: <12m; 12-23m; 24-59m; 5-14y; 15-64y; 65+	July 2008 to June 2016
Walk-in-Centre attendance records	Attendances to a Walk-in-Centres in Wirral, covering an estimated resident population of 320,000	Walk-in-Centre attendance for infectious gastroenteritis (Read Codes: gastroenteritis—presumed infectious origin (A0812), diarrhoea of presumed infectious origin (A083); infantile viral gastroenteritis (A07y1); infectious gastroenteritis (A0803); enteritis due to rotavirus (A0762); and infectious diarrhoea (A082)	All Walk-in-Centre attendances per month by age group	All ages: <12m; 12-23m; 24-59m; 5-14y; 15-64y; 65+	July 2011 to June 2016
GP practice records	Consultations at 136 GP practices in Merseyside, covering an estimated population of 790,000	Consultations for infectious gastroenteritis (Read Codes: as above for Walk-in-Centre)	Yearly estimated GP registered population by age group. Data were available from 2010 to 2016, therefore estimates for 2007/2008 and 2008/2009 were synthetically estimated using predictions from linear regression models. Source: Public Health England and participating GP practices	All ages: <12m; 12-23m; 24-59m; 5-14y; 15-64y; 65+	July 2007 to June 2016

6.3.4 Uptake of rotavirus vaccination

Pseudo-anonymised vaccine status data were extracted from the Child Health Information Service (CHIS) (232,233). The CHIS is managed locally by NHS Trusts and holds a unique record on each child born in these areas until the age of 18 years. We obtained a CHIS data extract on children eligible for rotavirus vaccination born from May 2013 to June 2016. The extract included a unique identifier, year and month of birth; year and month of first and second dose of rotavirus vaccine, and LSOA of residence. CHIS could be accessed for four out of the five local authorities in Merseyside. Data for Wirral could not be extracted due to lack of access to the CHIS database during the study period, related to organisational restructuring. We used codes in the CHIS dataset to exclude deaths, stillbirths and children who were born in Merseyside during the study period but subsequently moved out from the area.

6.3.5 Statistical analyses

Impact

We examined monthly hospitalisations / attendances to healthcare providers using an interrupted time-series design. Firstly, to predict counterfactual numbers of hospitalisations and attendances that would have been expected in the absence of vaccination for the vaccine period, we fitted generalised linear models with Poisson or negative binomial distributions (to account for over-dispersion in the data) to pre-vaccine introduction monthly counts, offset for dataset specific denominator (Table 6-1). We adjusted for seasonal trends by including a categorical term for calendar month and secular trends by including a linear term for surveillance year (July to June) as explanatory variables in the models. Secondly, to quantify the percentage reduction in monthly attendances / hospitalisations, we included all data pre- and

post-vaccine introduction in a second model with a binary indicator variable denoting the post-vaccine period. This second model also included the same terms to adjust for seasonal and secular trends and allowed the calculation of incident rate ratios (IRRs). Percentage reduction was calculated as: $100 \times (1 - IRR)$. The RVGE "season" in the UK in the pre-vaccine period was consistently between the months of January and May with the peak occurring in early to mid-March in most years;(36) for sensitivity analysis we examined specificity of end-point by stratifying by events which occurred in-season (January-May) and out-of-season (June-December). To investigate vaccine impact by age, the analysis was stratified by age group (<12 months, 12-23 months, 24-59 months, 5-14 years, 15-64 years, 65+ years and 0-59 months).

Socioeconomic deprivation, vaccine uptake and hospitalisations

Firstly, we wished to assess whether the incidence of all-cause AGE hospitalisations varied by level of socioeconomic deprivation. To achieve this we fitted negative binomial generalised linear models with the number of hospitalisations as the dependent variable and quintile of deprivation as the independent variable, offset for population denominator and adjusting again for seasonal and secular trends (model Y). Quintile of deprivation was calculated using the IMD scores for LSOAs nationally, whereby quintile five is the least deprived and quintile one the most deprived. Since the population of Merseyside is skewed towards the most deprived national quintiles, we combined the two least deprived quintiles into category "4/5 (least deprived)". The models allowed calculation of IRR for socioeconomic deprivation group by comparing the least deprived "4/5 (least deprived)" to the other quintiles, stratified by age group.

Secondly, we describe uptake of 1st and 2nd dose of rotavirus vaccine by month of birth for children born between May 2013 and December 2015. December 2015 was selected as the cut-off to allow all children in the cohort to reach 25 weeks of age, the upper time limit for rotavirus vaccination.(234) To investigate associations between socioeconomic deprivation and vaccine uptake, we fitted logistic regression models where the dependent variable was vaccine status and independent variable was national quintile of IMD and adjusted for gender, year and month of birth. The models allowed calculation of risk ratios (RRs) for socioeconomic deprivation group by comparing the least deprived "4/5 (least deprived)" to the other quintiles.

Finally, we estimated the all-cause AGE hospitalisations averted per 1,000 vaccine first doses delivered in the 2014/15 and 2015/16 seasons for vaccine eligible cohorts aged <12 months and 12-23 months. We define the rate of hospitalisations averted per 1,000 vaccine first doses delivered as:

$$RDA_{ijk} = \frac{X_{ijk} - Y_{ijk}}{P_{ijk}V_{ijk}}$$

where: RDA is the rate of hospitalisations averted per 1,000 vaccine first doses delivered; X is the model predicted counter-factual number of hospitalisations that would have been expected in absence of vaccination for the vaccine period; Y is the observed number of hospitalisations in the vaccine period; P is the population denominator; V is the proportion of the population vaccinated with one dose of vaccine; i is the deprivation group; j is the age group; k is the surveillance year.

We used the RDA in the Merseyside population in this study to provide an estimate of the number of all-cause AGE hospitalisations averted at a national level if the 95% vaccine uptake targets set by the World Health Organization (WHO) were

achieved across all deprivation strata (235,236). We define the total number of all-cause AGE hospitalisations averted at a national level in 2015/16 at uniform 95% uptake as:

$$NDA = \sum \frac{RDA_{ijk}}{1000} \times (N_{ijk} \times 0.95)$$

where: NDA is the number of all-cause AGE hospitalisations averted; RDA is the rate of hospitalisations averted per 1,000 vaccine first doses delivered in the Merseyside population; N is the national population denominator, derived from mid-year LSOA population estimates 2015 (230); i is the deprivation group; j is the age group; k is the surveillance year.

Data handling and analysis was conducted in R version 3.3.0 or later (224).

6.4 Results

6.4.1 Vaccine uptake

Rotavirus vaccine uptake (at least one dose of vaccine) in children born between May 2013 and December 2015 was 91.4% (29108/31,836); completion of full rotavirus vaccine schedule (i.e. two doses) was 86.7% (27,594/31,836). In the least deprived population, vaccine uptake for at least one dose was 93.6% (4,135/4,420) and 90.2% (3,989/4,420). For completion of the two dose schedule; in the most deprived population uptake was 90.6% (16,550/18,259) and 84.9% (15,505/18,259), respectively (Figure 6-1). The most deprived populations had a 54% (RR 1.54; 95% CI 1.34-1.75) increased risk of non-vaccination compared the least deprived populations. Furthermore, the most deprived populations had almost twice the risk (RR 1.97: 95% CI 1.62-2.41) of non-completion of the two dose schedule compared to the least deprived.

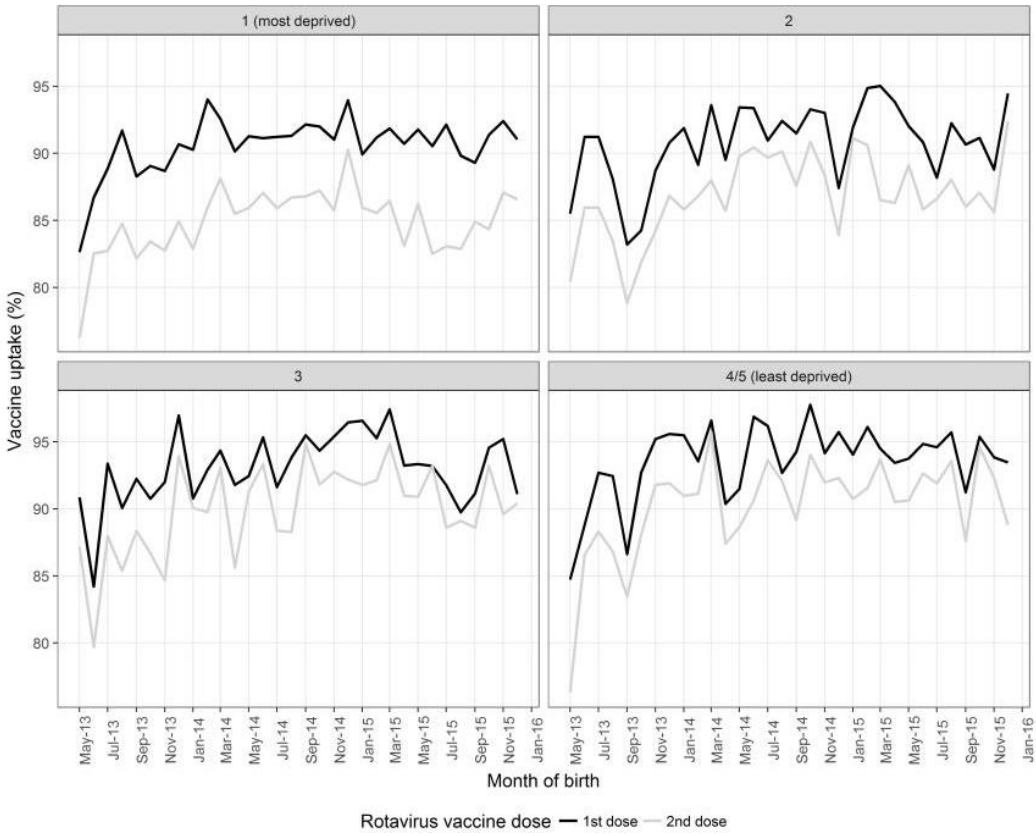

Figure 6-1. Rotavirus vaccine uptake in 4/5 areas of Merseyside for children born between May 2013 and December 2015 by deprivation quintile

6.4.2 Vaccine impact by age

Impact in under 5 year olds

In children less than 5 years of age a clearly defined rotavirus season was observed prior to vaccine introduction, with the peak predominately occurring in March across all outcome measures for all years prior to vaccine introduction (Figure 6-2). The incidence of gastrointestinal disease fell across all health outcomes following vaccine introduction (Figure 6-2; Table 6-2). The greatest proportional reduction, 80% (95% CI 70-87%), was for RVGE hospitalisation. All-cause AGE hospitalisations fell by 44% (95% CI 35-53%), ED attendances for gastrointestinal conditions by 23% (95% CI 11-33%); and WIC and GP consultations for infectious gastroenteritis by 32% (95% CI 7-50%) and 13% (95% CI -3 to 26%), respectively. Reductions were greatest in the rotavirus season for all outcomes; all-cause AGE

hospitalisations fell by 58% (95% CI 45-67%) and GP consultations by 29% (95% CI 8-45%).

Disease reductions were highest in vaccine eligible age groups. RVGE hospitalisation fell by 87% (95% CI 78-93%) in infants age <12 months and 84% (95% CI 73-91%) in children 12-23 months; all-cause AGE hospitalisations fell by 46% (95% CI 36-54%) in infants <12 months and 50% (95% CI 40-59%) in children 12-23 months. In GP practices, infectious gastroenteritis consultations fell by 19% (95% CI 4-33%) in infants, averting 136 consultations per 10,000 registered population. There were also significant reductions in gastrointestinal disease outcomes in vaccine age ineligible children age 24-59 months; RVGE hospitalisations decreased in this age group by 66% (95% CI 44-81%) and all-cause AGE hospitalisations decreased by 26% (95% CI 11-39%). However, in the 2014/15 season a peak of incidence was detected in May across all primary outcome measures that was comparable in magnitude to the pre-vaccine rotavirus peak observed in March. Disease rates by surveillance year and pre- and post-vaccine introduction are provided in Appendix C: Table S3.

Impact in children aged 5 to 14 years

In the pre-vaccine period, children aged 5-14 years had the lowest yearly rates of hospitalisation for all-cause AGE (18 per 10,000 population) (Table 6-2). Rotavirus seasonality in children aged 5-14 years, was less pronounced and inconsistent across all outcome measures in the pre-vaccine period (Figure 6-2). In this vaccine-ineligible age group, between July 2013 and June 2016 there were only two laboratory confirmed detections of RVGE at Alder Hey Children's hospital. Furthermore, all-cause AGE hospitalisations and ED attendances for gastrointestinal conditions also fell (Table 6-2). General Practice consultations (-3%, 95% CI -21 to

12%) and WIC attendances (0 %, 95% CI -52 to 34%) for infectious gastroenteritis remained similar to pre-vaccine levels. There were no differences between changes in incidence in the rotavirus-season and out of the rotavirus-season.

Impact in persons aged 15-64 years

Data were available for four out of five of the primary outcomes. There was no clearly identified seasonality in the pre-vaccine period for the non-specific outcome measures in this age group (Figure 6-3). Moderate reductions were seen in persons aged 15-64 years across all outcome measures (Table 6-2). In the post-vaccine period hospitalisations for all-cause AGE fell by 8% (95% CI 2-14%), ED attendances for gastrointestinal conditions by 29% (95% CI 16-40), and WIC and GP consultations for infectious gastroenteritis by 24% (95% CI 16-40%) and 26 % (95% CI 18-33%), respectively. There were no significant differences in the level of percentage change when comparing in season and out of season periods.

Impact in 65+ year olds

There were significant, moderate reductions in all-cause AGE hospitalisations, ED attendances for gastrointestinal conditions and GP consultations for infectious gastroenteritis (Figure 6-3; Table 6-2). The reduction in attendances to WICs for infectious gastroenteritis was non-significant (47%, 95% CI -15 to 75%). The absolute rate of consultations prevented was 19 per 10,000 registered population for GPs and 34 per 10,000 for WICs (Table 6-2). During the rotavirus season, proportional reductions were slightly higher than out of season, although the difference was not significant.

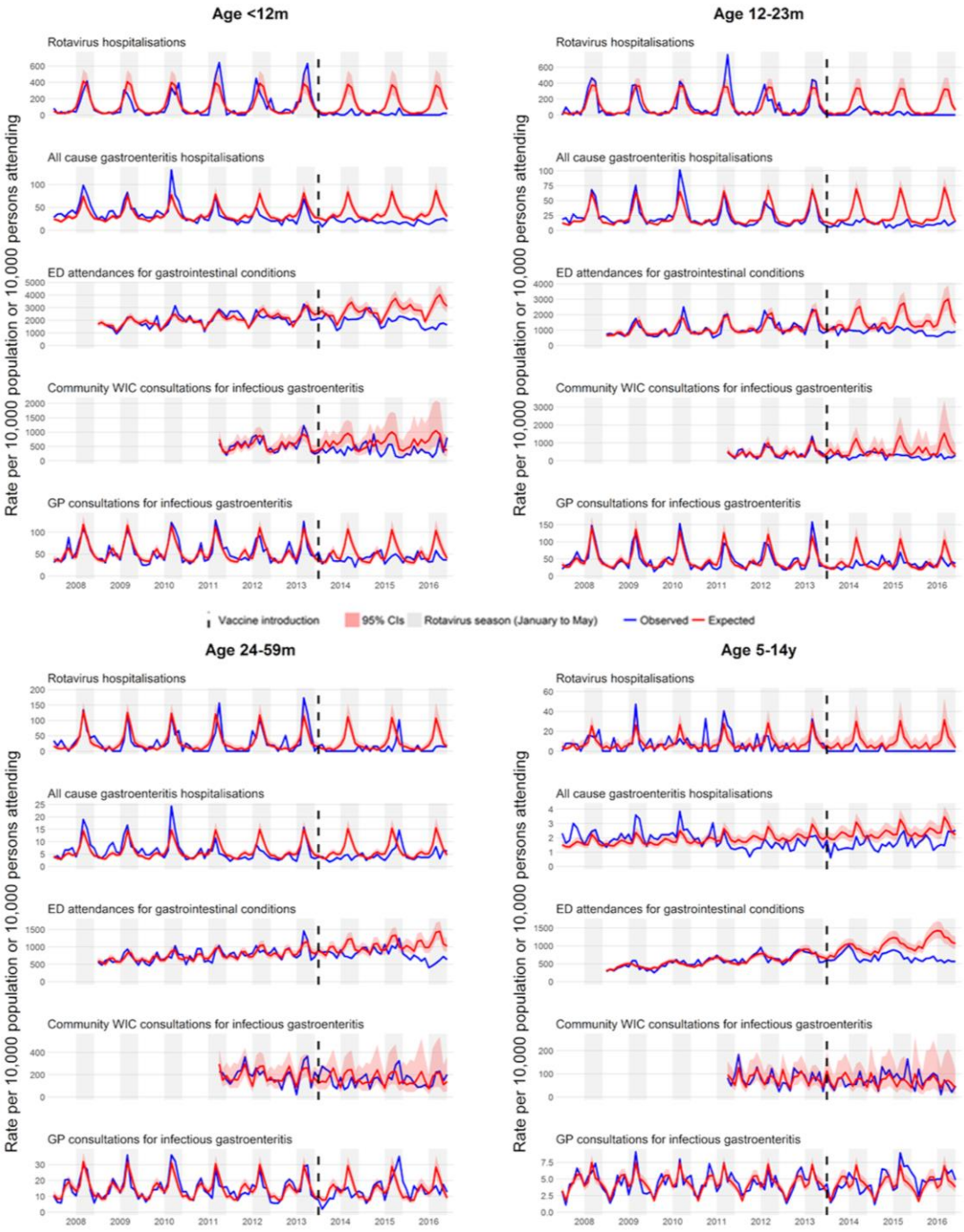

Figure 6-2. Trends in five study outcome measures for children aged 0-14 years in Merseyside, UK, July 2008 to June 2016 [Each analysis examines trends, including comparison of observed incidence (blue line) after rotavirus vaccination (July 2013 to June 2016) in the UK with expected incidence (red line) and associated 95% confidence intervals (red shaded area) in the absence of vaccination. Expected incidence and 95% confidence intervals are based on predictions from regression models fitted to available historic data for each outcome measure. The black hashed line represents the introduction of rotavirus vaccine in the UK in July 2013]

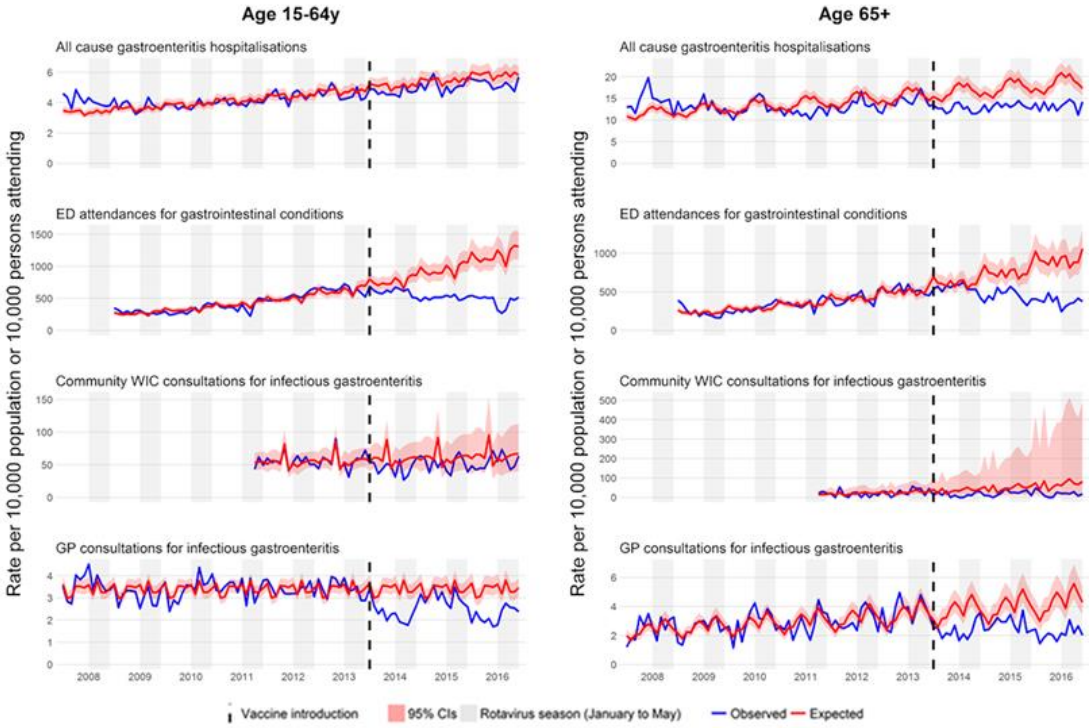

Figure 6-3 Trends in four study outcome measures for older children and adults aged 15+ years in Merseyside, UK, July 2008 to June 2016 [Each analysis examines trends, including comparison of observed incidence (blue line) after rotavirus vaccination (July 2013 to June 2016) in the UK with expected incidence (red line) and associated 95% confidence intervals (red shaded area) in the absence of vaccination. Expected incidence and 95% confidence intervals are based on predictions from regression models fitted to available historic data for each outcome measure. The black hashed line represents the introduction of rotavirus vaccine in the UK in July 2013]

Table 6-2. Changes in rates of hospitalisation / attendances to different levels of the health system post rotavirus vaccine introduction in Merseyside, UK

Age group	Mean yearly rate of hospitalisations / attendances (per 10,000)[¥]			Percent reduction in hospitalisations / attendance rates (95% CI)†		
	pre-vaccination	post vaccination				
	Observed	Observed	Expected*	Full year	Jan-May	Jun-Dec
Hospitalisations for laboratory confirmed rotavirus to Alder Hey						
<12m	129	14	122	87 (78 - 93)	94 (86 - 97)	57 (10 - 81)
12-23m	123	16	106	84 (73 - 91)	87 (76 - 94)	70 (19 - 91)
24-59m	33	10	29	66 (44 - 81)	74 (52 - 87)	35 (70 - 77)
5-14y	7	0.3	9	95 (84 - 99)	96 (80 - 99.7)	94 (71 - 99.7)
Total 0-59m	87	12	81	80 (70 - 87)	88 (80 - 94)	58 (25 - 77)
Hospitalisations for all cause acute gastroenteritis						
<12m	402	230	468	46 (36 - 54)	60 (49 - 69)	35 (20 - 46)
12-23m	271	128	311	50 (40 - 59)	66 (56 - 74)	37 (19 - 50)
24-59m	72	54	78	26 (11 - 39)	33 (10 - 50)	22 (1 - 38)
5-14y	18	20	28	32 (21 - 41)	35 (19 - 48)	29 (13 - 42)
15-64y	39	60	66	8 (2 - 14)	11 (1 - 19)	6 (1 - 13)
65+	135	157	210	25 (19 - 30)	28 (19 - 36)	22 (15 - 29)
Total 0-59m	178	104	213	44 (35 - 53)	58 (46 - 67)	35 (22 - 46)
ED attendances for gastrointestinal conditions (no admission)						
<12m	2034	1855	2816	22 (11 - 33)	30 (15 - 42)	16 (2 - 29)
12-23m	1146	892	1650	31 (15 - 43)	41 (19 - 57)	23 (4 - 38)
24-59m	759	759	1054	12 (-4 - 25)	14 (-15 - 36)	10 (-6 - 24)
5-14y	552	661	1038	22 (11 - 31)	17 (-2 - 33)	25 (12 - 36)
15-64y	405	503	993	29 (16 - 40)	30 (4 - 49)	28 (14 - 40)
65+	341	438	788	21 (4 - 34)	25 (-5 - 46)	18 (-3 - 34)
Total 0-59m	1235	1124	1795	23 (11 - 33)	31 (12 - 45)	18 (4 - 29)
Walk-in centre attendances for infectious gastroenteritis						
<12m	574	373	644	37 (6 - 58)	51 (12 - 73)	25 (-26 - 55)
12-23m	463	256	606	39 (0 - 63)	67 (38 - 83)	5 (-86 - 52)
24-59m	196	153	167	18 (-20 - 44)	36 (-12 - 64)	-5 (-79 - 38)
5-14y	79	71	68	0 (-52 - 34)	6 (-77 - 49)	-6 (-86 - 39)
15-64y	55	51	61	24 (7 - 38)	29 (0 - 49)	21 (-4 - 40)
65+	22	18	52	47 (-15 - 75)	56 (-43 - 86)	38 (-72 - 78)
Total 0-59m	362	231	363	32 (7 - 50)	51 (22 - 69)	12 (-27 - 39)
GP consultations for infectious gastroenteritis						
<12m	674	492	628	19 (4 - 33)	40 (27 - 51)	3 (-20 - 21)
12-23m	590	418	498	13 (-10 - 31)	38 (11 - 56)	-11 (-44 - 14)
24-59m	184	166	172	8 (-14 - 26)	7 (-29 - 33)	9 (-20 - 31)
5-14y	53	56	51	-3 (-21 - 12)	-7 (-38 - 17)	0 (-23 - 19)
15-64y	41	30	41	26 (18 - 33)	29 (17 - 40)	23 (13 - 32)
65+	35	29	48	36 (25 - 45)	43 (30 - 54)	30 (13 - 43)
Total 0-59m	363	282	331	13 (-3 - 26)	29 (8 - 45)	0 (-20 - 17)

*Expected in the absence of vaccination using negative binomial or Poisson model adjusting for month and rotavirus year for the pre-vaccine years. †percent change is calculated as 1-risk ratio. Risk ratio was calculated using a negative binomial model adjusting for month and rotavirus year. [¥]Table 6-1 provides specific denominators for each outcome measure

6.4.3 Vaccine impact by socioeconomic deprivation status

Burden of gastrointestinal infection prior to vaccine introduction

Prior to vaccine introduction the risk of being admitted to hospital for all-cause AGE was 57% higher (IRR=1.57, 95% CI 1.51-1.64) in the most socioeconomically deprived populations of Merseyside compared to the least (Figure 6-4). Age group stratified analyses showed that in all age groups apart from those 5-14 years of age (IRR=1.08, 95% 0.96-1.21), the risk of hospitalisation with all-cause AGE was significantly greater in the most socioeconomically deprived populations of Merseyside compared to the least. Children <12 months of age in the most socioeconomically deprived quintile had the highest rate of hospitalisation (47 per 1,000 person years), compared with 36 per 1,000 person years in the least deprived (IRR=1.31, 95% 1.16-1.47). Among 12-23 month olds, the age group with the second highest rates of hospitalisation, the difference between the most deprived (30 per 1,000 person years) and least deprived (26 per 1,000 person years) was less pronounced (IRR=1.15, 95% CI 1.01-1.31).

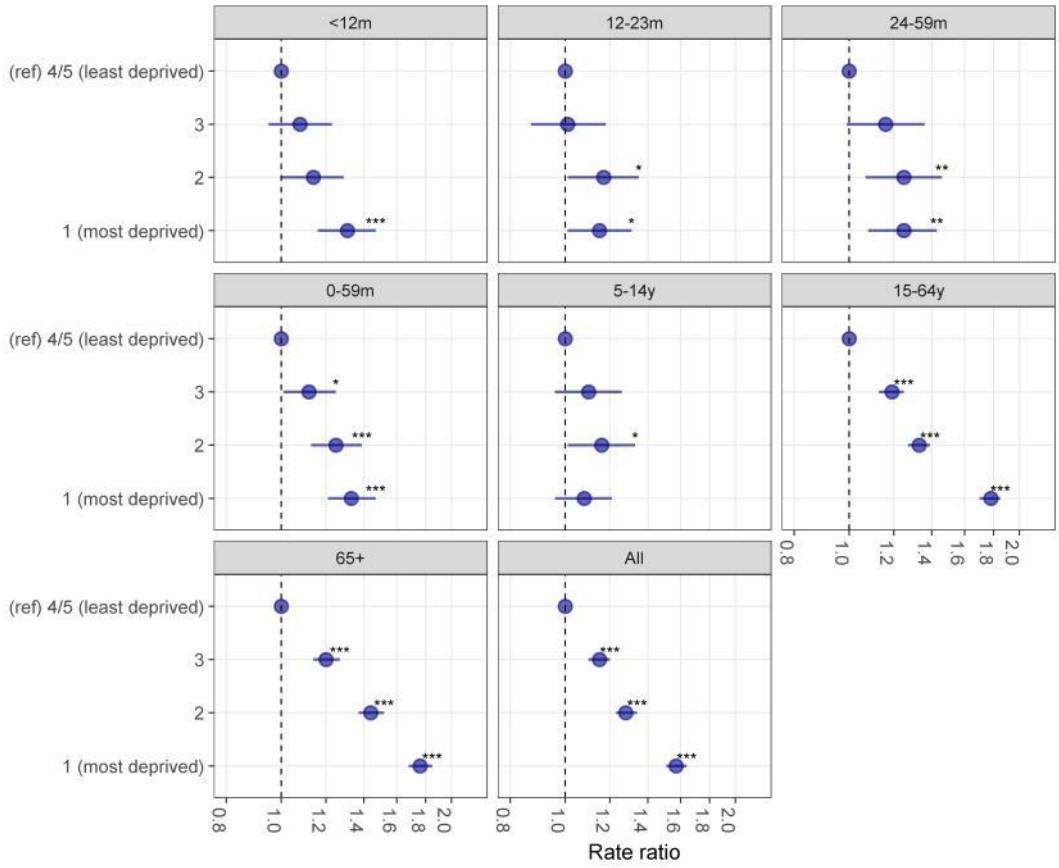

Figure 6-4 Incidence rate ratios of hospitalisation with acute all cause-gastroenteritis prior to vaccine introduction, by age group and deprivation quintile, July 2004 to June 2013, Merseyside UK

Hospitalisations averted per child vaccinated

We estimated the number of all-cause AGE hospitalisations potentially averted in Merseyside due to rotavirus vaccination in two vaccine eligible age cohorts, <12 months and 12-23 months of age. In children aged <12 months living in the most deprived populations it was estimated that in 2014/15 and 2015/16, 28 (95% CI 25-31) and 26 (95% CI 23-30) all-cause AGE hospitalisations were averted per 1,000 1st dose rotavirus vaccines delivered, respectively. In the least deprived populations 15 (95% CI 12-17) and 13 (95% CI 11-16) all-cause AGE hospitalisations were averted per 1,000 rotavirus vaccine 1st dose delivered, in 2014/15 and 2015/16 respectively (Figure 6-5). For the cohort aged 12-23 months it was estimated that there were 18

(95% CI 15-20) all-cause AGE hospitalisations averted per 1,000 persons vaccinated with at least one dose of rotavirus vaccine in 2015/16 in the most deprived populations, and 13 all-cause AGE hospitalisations averted (95% CI 11-16) in the least deprived populations.

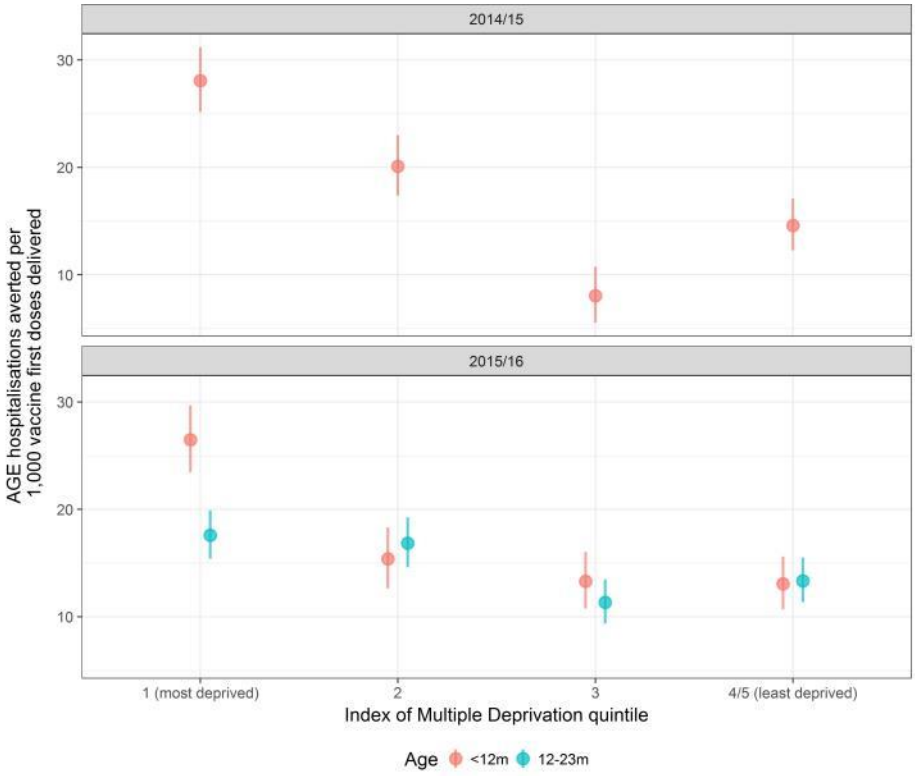

Figure 6-5 Estimated all-cause acute gastroenteritis hospitalisations averted per 1,000 vaccine first doses delivered in the 2014/15 and 2015/16 seasons for vaccine eligible cohorts aged <12 months and 12-23 months [AGE, acute gastroenteritis]

If the WHO target for primary childhood immunisations of 95% uptake were attained in each deprivation strata nationally (England), 10,810 all-cause AGE hospitalisations in infants would have been averted in 2015/16, with 41% (4,395, 95% CI 3,898-4,925) of those averted in the most deprived population (Table 6-3). Among 12-23 month olds 9,472 all-cause AGE hospitalisations would be expected

to be averted, with 31% (2,940, 95% CI 2,570-3,330) of those averted in the most deprived population.

Table 6-3 Predicted all-cause acute gastroenteritis hospitalisations averted nationally in children under 2 years of age in 2015/16 at 95% vaccine uptake

Age group	Index of Multiple Deprivation	Estimated national population (2016)	Hospitalisations averted at 95% vaccine uptake		
			N	95% LCI	95% UCI
<12months	1 (most deprived)	174784	4395	3898	4925
	2	149462	2185	1795	2603
	3	126372	1597	1292	1924
	4/5 (least deprived)	212359	2634	2156	3147
	Total	662977	10810		
12-23 months	1 (most deprived)	176129	2941	2579	3330
	2	149862	2397	2080	2740
	3	126517	1363	1124	1621
	4/5 (least deprived)	218485	2771	2359	3218
	Total	670993	9472		

6.5 Discussion

In this study to simultaneously evaluate the impact of rotavirus vaccine introduction across all levels of the healthcare system in a defined geographic area, we have demonstrated reductions in gastrointestinal disease burden across all levels of healthcare and across all ages. Reductions were greatest for the most specific and severe disease outcomes (rotavirus and hospitalisations), during the rotavirus season, and for the youngest children who were vaccine age-eligible. Smaller reductions among older, unvaccinated populations suggest herd protection. The impact of vaccination was also greater in the most socioeconomically deprived populations, despite lower vaccine coverage.

Most previous studies that evaluated rotavirus vaccine impact in high income countries focussed on severe disease outcomes, with magnitude of reductions similar to those described here in both vaccine eligible and ineligible children (134,141,145,147–149,223,237–244). The reduction in all-cause AGE of 46% (36-55%) for infants and 50% (38-60%) for children 12-23 months of age was also similar to that reported in earlier UK studies, as was the indication of herd protective effects in older adults and children (223,239).

For less severe disease outcomes (disease presenting to GPs and WICs) we demonstrated smaller relative reductions compared to more-specific or severe disease outcomes. However, these reductions constitute a substantial contribution to the absolute number of healthcare contacts averted through vaccination. The impact on non-specific outcome measures was consistently highest during the rotavirus season for children under five years, suggesting that the observed reduction in incidence of AGE is likely to be due to a real reduction in rotavirus disease. The smaller reductions in consultations in primary care (WICs and GP practices) are likely explained by the non-specific gastroenteritis outcome measure and also because of the presumed lower effectiveness of rotavirus vaccine against milder disease (98,203). Furthermore, the reductions in GP consultations for infectious gastroenteritis observed in vaccine age-eligible children (19% for infants and 13% for 12-23 months) are epidemiologically plausible, since a study from the pre-vaccine period estimated that rotavirus was detected by enzyme-linked immunosorbent assay (ELISA) in 14%, and by ELISA and / or PCR in approximately 19% of infectious intestinal disease GP consultations in UK children under 5,(47,245) with this estimate likely to be higher in infants. Furthermore, the estimated reductions in WIC attendances and GP consultations are comparable to

that reported from analysis of UK syndromic surveillance of GP consultations for gastroenteritis, diarrhoea, and vomiting (26% reduction in infants),(228) and are comparable with reductions in AGE outpatient attendances reported in Finland (13% reduction in infants) (146,148).

We have shown that the most deprived populations were at the greatest risk of all-cause AGE prior to vaccine introduction, with highest rates of disease occurring in infants in the most deprived populations. This supports previous findings from a lower resolution national study, which showed that the rate of hospitalisation with all-cause AGE increased with increasing deprivation.(159) The uptake of rotavirus vaccination in our study population was also associated with neighbourhood level deprivation, with significantly lower uptake of the 1st dose of vaccine and lower completion of the full 2 dose schedule in the most deprived populations. Similar findings have been shown in Merseyside for measles, mumps and rubella vaccination, and locally and nationally for childhood influenza vaccination (160,161).

We were able to overlay a combination of small area level deprivation status, vaccine uptake and all-cause AGE hospitalisations to estimate the disease averted per 1st vaccine dose delivered for different deprivation strata. In infants, disease averted by vaccination was higher in the most deprived, suggesting that even with lower vaccine uptake the most deprived populations benefit the most from the vaccination programme. The higher rates of disease averted in infants <12 months of age living in the most deprived populations is likely to reflect the higher baseline burden of disease in this group and the relative inequity of hospitalisation rates prior to vaccine introduction. However, in the 12-23 month olds there a smaller difference in disease averted between the least deprived and the most deprived reflecting the lower baseline inequity in disease burden between the deprivation strata.

Nationally there are disproportionately more infants and young children living in the most deprived quintile (26%) compared to the least deprived (15%).(229,230) With individual level vaccine effectiveness known to be lower in persons with lower socioeconomic status in studies conducted in high income settings,(174,246) improving vaccine uptake in the most deprived populations will have the biggest impact towards reducing rotavirus associated disease. We estimate that over 41% of all-cause AGE hospitalisations averted in infants due to rotavirus vaccination would be averted in the most deprived populations if vaccine uptake was equitable across deprivation strata at the WHO vaccine uptake target of 95% (235,236).

6.5.1 Strengths and Limitations

This ecological study using routine health service data is subject to a number of limitations. There is an inherent problem with clinical coding of RVGE in UK hospitals; quality analysis at Alder Hey Children's hospital showed that only 39% of laboratory confirmed rotavirus hospitalisations were coded as ICD10 rotaviral enteritis (A08.0), and this figure is lower in other UK based hospitals (247).

Since rotavirus detection is not routinely undertaken in community settings such as GP and WICs, syndromic and non-specific outcomes related to gastroenteritis were used, and we were therefore unable to account for the contribution of other pathogens causing AGE. However, the predictable seasonality of rotavirus infection allowed analysis to focus on the rotavirus season, which should improve the robustness of reduction estimates in age-eligible children. In older children and adults the estimates are more uncertain because there is limited laboratory testing and surveillance data on rotavirus seasonality and disease burden in these age groups in the pre-vaccine period. The lack of routine testing is evidenced by the recommendation in the Standards for Microbiology Investigation S7: gastroenteritis

and diarrhoea (PHE) that rotavirus testing is only standard for sporadic cases of gastroenteritis under the age of 5 years and immunocompromised cases (26).

Because of these limitations, model fit was less good for older populations due to the less seasonal and more random incidence of gastroenteritis disease, and in these situations the analysis may have overestimated the impact of vaccination. Furthermore, we used non-dynamic regression fit and so were not accounting for changes in force of infection due to reduction in number of cases. We were therefore not able to adjust the predicted incidence to account for current levels of infection. A full transmission model would be required to fully describe the reduction in transmission rate and associated case reduction due to vaccination. Despite these limitations, studies in the UK, Australia, Europe and the US also show impact in older populations (134,143,223,239,240,248,249). The number of hospitalisations averted nationally under uniform 95% vaccine uptake was made using two main assumptions. Firstly, that the population of Merseyside is representative of the population nationally and secondly, that the relationship between vaccine uptake and the herd protective effect of vaccination is linear. Therefore the estimates are likely to be conservative as a consequence of assuming a linear relationship, particularly if the level of rotavirus vaccine uptake required for population protection is reached before 95% uptake.

Finally, the novelty of measuring vaccine impact on multiple levels of a health system simultaneously in a defined population provides robustness that any detected changes are due to rotavirus vaccination rather than idiosyncrasies of one particular dataset. For example we detected delayed peak activity (April / May) in children aged 24-59 months across all primary outcome measures in season 2014/15 strengthening the evidence that the datasets used in this study were useful in

detecting rotavirus activity in non-specific outcomes. This delayed peak is also observed in laboratory confirmed rotavirus detections nationally.

6.5.2 Conclusions and policy implications

This analysis identified the effect of rotavirus vaccination on healthcare utilisation for acute gastroenteritis in the four major levels of the UK health system for five outcomes of varying specificity. The study strongly indicates that rotavirus vaccination has reduced the incidence of acute gastroenteritis across the healthcare system in both vaccine eligible and ineligible populations. Rotavirus vaccination will therefore contribute to alleviating the increasing pressures on acute services across a health system. With impact greater than that predicted through cost effective modelling in the UK (222), these data strongly support the sustained use of the vaccine in the UK and continued expansion to other European countries.

We have also shown that prioritising vaccine uptake in the most socioeconomically deprived communities is likely to give the greatest health benefit in terms of population disease burden and can contribute to reducing health inequalities. Further studies are required to disentangle which factors related to socioeconomic deprivation have greatest influence over vaccine acceptance, so that interventions to improve vaccine uptake can be effectively targeted.

7 Mitigating confounding in observational vaccine effectiveness studies: a novel methodology using propensity score estimation to balance comparator populations in a rotavirus vaccine evaluation

7.1 Abstract

Background: Measuring real world vaccine effectiveness (VE) relies on the use of observational study designs. However, achieving robust estimates of direct and indirect VE is frequently compromised by bias, particularly when using syndromic diagnoses of low-specificity.

Methods: In order to mitigate confounding between the measured outcome and the likelihood of being vaccinated we developed a method to balance comparator populations using individual-level propensity scoring derived from the vaccine-exposed population, and applied it to the unexposed comparator population. Indirect VE was estimated by comparing the unvaccinated vaccine-exposed group with a propensity score-simulated unvaccinated, unexposed group. Direct VE was derived by removing indirect VE from the overall VE. We applied this method we applied it to data collected for evaluation of rotavirus vaccine introduction in the UK in July 2013. In a general practice birth cohort covering the period May 2010 and June 2016 and including 54,548 births, we calculated indirect and direct VE against consultations for acute gastroenteritis using conventional and vaccination-propensity adjustment comparator populations.

Results: The overall VE calculated using mixed effects Cox regression was 11% [95% confidence intervals (95% CIs): 7-16%]. Use of traditional comparator populations resulted in implausible VE estimates of -46% (95% CIs: -70 to -26%)

for direct and 34% (95% CIs: 23-43%) for indirect effects. Applying our alternative method and estimating VE at a range of propensity scores, direct VE ranged between 8 and 11% and indirect VE between 1% and 4%.

Conclusions: Estimating VE using propensity score simulated comparator populations, particularly for those studies using routine health data with syndromic, low-specificity endpoints will aid accurate measurement of the broader public health impact of a vaccine programme.

7.2 Background

Vaccine efficacy is best measured by randomised controlled clinical trials (RCTs); such trials are considered to be the gold standard and are often conducted prior to vaccine licensing. However, efficacy studies have rigorously controlled conditions and are only generalisable if the study population is comparable to the wider population. In contrast, vaccine effectiveness (VE) is a measure of vaccine performance under real world conditions (80). Commonly a case-control or cohort design is used for calculating VE. These designs have the benefit of being cheaper than RCTs. Whilst RCTs with individual randomisation allow the calculation of direct vaccine efficacy, VE studies enable the calculation of the overall VE as an indicator of the public health benefit of a vaccine. Overall VE is a composite of the direct effect on those vaccinated and indirect effect / herd protection conferred by the vaccine on the unvaccinated; the total effect combines the direct and indirect effect in only those that are vaccinated (Figure 7-1). The overall VE and the indirect effect are important for the measurement of the broader public health impact, allowing health authorities to calculate realistic vaccine cost-effectiveness, informative to vaccine programmes (77,74,76,250).

Halloran et al., provide a framework for study design to allow calculation of the constituents of overall VE in observation studies (Figure 7-1) (77). This methodology has been referenced in a number of observational VE studies (85,106,251) In Halloran's approach two populations are compared, population A-'vaccine-exposed' and comparator population B-'unexposed'. Population A and B must be separate in space and/or time to ensure no transmission between populations. Population A is divided according to individual vaccination status into A_1 (vaccinated) and A_0 (unvaccinated). Furthermore, this method requires that populations A_1, A_0, and B are similar in base-line population and individual level characteristics and be distinguished only by vaccine receipt. In observational post-licensure studies particularly those that utilise healthcare databases for VE estimation, are subject to selection bias: confounding introduced through different baseline characteristics of the population sampled, such as differences in healthcare access, health-seeking behaviour and social-mixing rates (80,252–254). Hence, an accurate calculation of the direct VE using post-vaccine population A, requires that the unvaccinated and vaccinated populations (A_0 and A_1, respectively) are comparable; indistinct in every aspect except vaccine receipt, if confounding is to be minimised (Figure 7-1). However, there is clear potential for confounder-dependent association between the outcome of interest and likelihood of being vaccinated (80,254). For example, those vaccinated (A_1) are likely to have different health-seeking behaviours and better healthcare access than those unvaccinated (A_0), particularly in outpatient or general practice (GP) settings (80,253). This will introduce ascertainment bias which may cause under-estimation of the direct effect (254). Additionally, due to social-mixing and transmission within the community, individuals in each population (A_0 and A_1) may not have fully independent infection

risks. Thus direct effect estimates from comparison between these groups is prone to error.

Estimating indirect and total effects by comparing either an unvaccinated post-vaccine population (A_0) or a vaccinated post-vaccine introduction population (A_1) with a temporally or geographically separate population B will not be appropriate. This is because population A has been conditioned on vaccine uptake, allowing for a distinction between populations A_0 and A_1. This is not the case for population B, which remains mixed, and incorporates residual confounding (76,80). Categorising population B into virtual groups, those that probably would and would not have received vaccine, offers a potential solution.

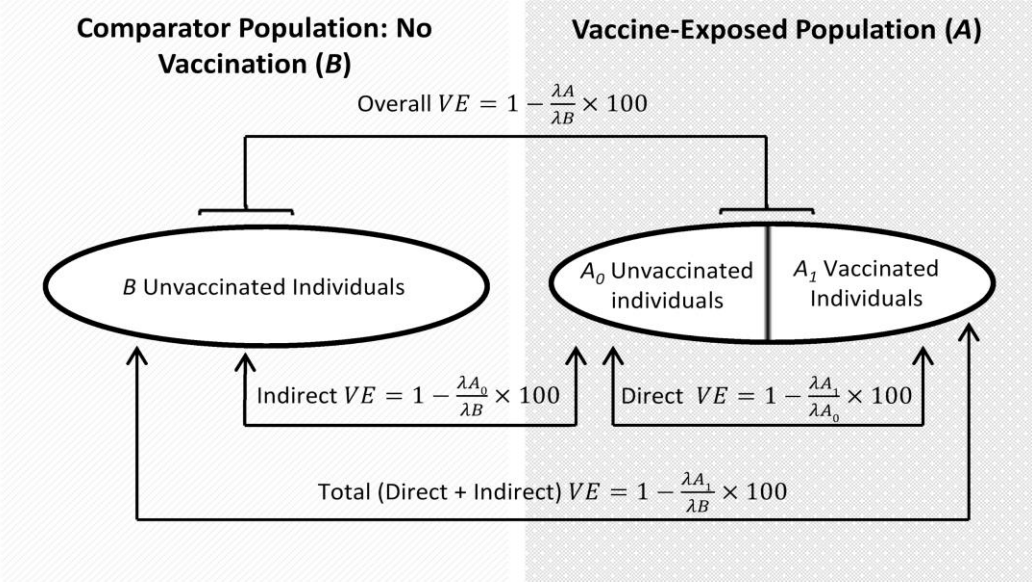

Figure 7-1 Calculation of vaccine effectiveness based on different comparison populations [Adapted from Halloran et al. 1997 and Panozzo et al. 2014 (77,85). Abbreviations: VE, vaccine effectiveness; λ, hazard rate of infection]

The limitations affecting accurate calculation of VE in many observational studies can be minimised through the use of propensity scores (PSs). The PS is traditionally used in observational studies to reduce the effect of confounding and is the

conditional probability of receiving treatment or of being exposed in relation to known baseline characteristics (255–258). We therefore propose the use of PS analysis to establish propensity for vaccine uptake in population A and then applying PS to population B. This enables the simulated splitting of population B into two groups; those who would have been likely to receive vaccine were it available (B_1) and those likely to remain unvaccinated despite vaccine availability (B_0) (Figure 7-2). Comparing A_0 with B_0 provides an estimate of indirect VE. Direct VE is then derived by removal of the indirect VE from the overall VE estimates. This method is particularly applicable to observational studies measuring the broader public health effect of a well utilised vaccine using non-pathogen specific syndromic endpoints where risk of bias is magnified. To provide an example of this methodology in practice we applied it to an evaluation of rotavirus vaccination in the UK.

7.2.1 Applied use of vaccination-propensity adjustment

Rotavirus vaccination was introduced into the childhood immunisation schedule for the UK in July 2013. Children born from 1st May 2013 were eligible to receive the live-attenuated, two dose oral monovalent rotavirus vaccine (RV1, Rotarix™, GlaxoSmithKline Biologicals S.A., Belgium) with doses given at two and three months of age (158). Rotavirus vaccination rapidly achieved high uptake, at over 92% for one dose and 88% for two by early 2014 (259). Impact studies in the UK have estimated reductions of over 70% in laboratory detections of rotavirus and >80% for rotavirus gastroenteritis hospitalisations since vaccine introduction (223,227,260). Although high-specificity disease endpoints (e.g. rotavirus gastroenteritis) are important, low-specificity endpoints (e.g. all-cause gastroenteritis) pose a significant burden to health systems because of their greater number. We therefore conducted a birth cohort study to assess VE against milder,

non-specific gastroenteritis presenting at GP. We firstly examined rotavirus VE using the study design comparator populations used in Figure 7-1 (Method One) and subsequently applied novel methodology to measure VE utilising PS analysis (Method Two) (Figure 7-2).

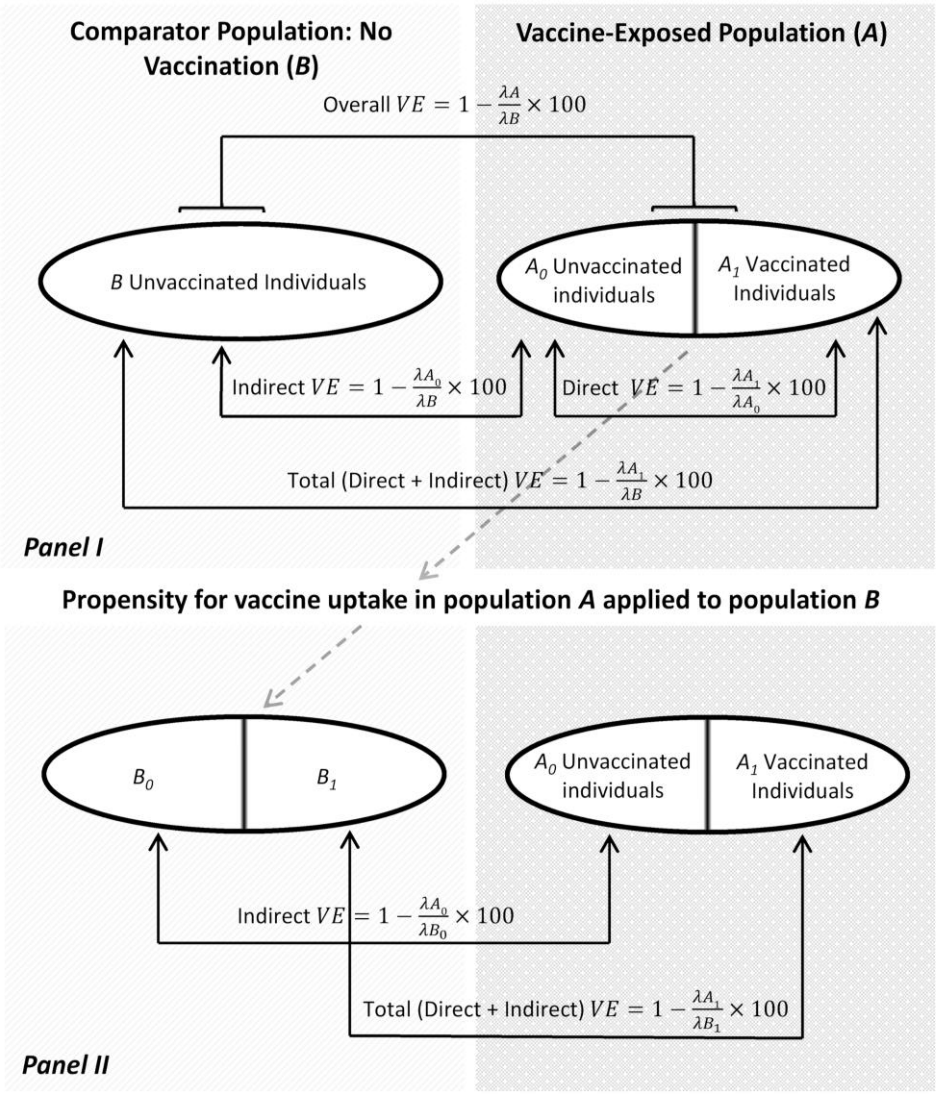

Figure 7-2. Calculation of vaccine effectiveness based on simulated comparison populations generated through the use of vaccination-propensity adjustment

[Population A and B are separate through *inter alia*, geographical or temporal separation. *Panel I* represents VE calculations under rigorously controlled or "idealised" real world conditions, with no difference other than receipt of vaccine between populations. *Panel II* represents vaccination-propensity adjustment for identifying comparator populations under observational conditions. (*Panel I*: adapted from Halloran et al. 1997 and Panozzo et al. 2014). Abbreviations: VE, vaccine effectiveness; λ, hazard rate of infection]

7.3 Study population and data

7.3.1 Setting

Merseyside is a large metropolitan area in England, with an estimated resident population in 2015 of 1.4 million persons, of whom 50,000 are under 3 years of age (261).

7.3.2 Design, Data and Population

In the UK, GPs electronically record consultations and patient notes for each patient registered. Children are routinely registered with a GP in the first months of life. We created a birth cohort dataset that included all children born between May 2010 and June 2016 and who were registered with any of the participating GPs. Data were extracted from GP records by practice or centrally via a National Health Service (NHS) Clinical Commissioning Group (CCG). Agreement to participate was first sought from the CCGs information governance and then GPs within the participating CCGs. Children entered the study at 6 months of age, beyond which no further rotavirus vaccination is given in the UK. Due to patient confidentiality data were not extracted from children that had died or children for whom there was no consent to share data.

7.3.3 Outcomes, exposures and covariates

Outcome measures were consultations for acute gastroenteritis including rotavirus gastroenteritis. Rotavirus coded consultations are rare because laboratory testing for rotavirus is not routinely undertaken in primary care. We therefore used coding indicating acute gastroenteritis and associated syndromes (*e.g.* diarrhoea), excluding those for specific non-rotavirus infections, as previously reported (214).

Vaccine status was extracted including date of vaccination (214); vaccine status was taken at six months of age. Six months was selected because the cut-off for receipt of the second dose of the vaccine in the UK is 24 weeks of age (262).

To account for geographical variation, we included an indicator for neighbourhood area of residence (Lower Super Output Area [LSOA]); in order to characterise differences in care seeking or access to healthcare we also included GP for which each child was registered. English LSOAs are small statistical boundaries consisting of approximately 1,500 people. Using LSOA of residence, a measure of socioeconomic deprivation was assigned to each participant, measured using English indices of deprivation, Index of Multiple Deprivation (229).

7.4 Statistical analysis

7.4.1 Method One

For time to first event analysis we used mixed-effects Cox proportional hazards regression models to estimate hazard ratios, comparing the hazard of acute gastroenteritis consultations in the pre-vaccine introduction cohort (B) to that in the post-vaccine introduction cohort (A) (Figure 7-1 and Figure 7-3). Overall VE ($A\ vs\ B$) was calculated using $1 - HR$. The time variable started at 0 days when children entered the cohort at 6 months of age and were censored following a consultation for acute infectious gastroenteritis or at the end of the study period; June 30th 2013 for the pre-vaccine cohort and June 30th 2016 for the post-vaccine period, whichever occurred first. The model included a random effect for registered GPs and was adjusted for gender and Index of Multiple Deprivation score. We also estimated the direct ($A_0 vs\ A_1$), indirect ($A_0 vs\ B$) and total effects ($A_1 vs\ B$), changing the comparison cohorts as described above (Figure 7-1). By way of sensitivity analysis, we examined the effect of specificity of endpoint by also fitting models which only

included events that occurred in peak rotavirus-season (January to May) because of the distinct seasonality of rotavirus disease in children in the UK prior to vaccine introduction (36).

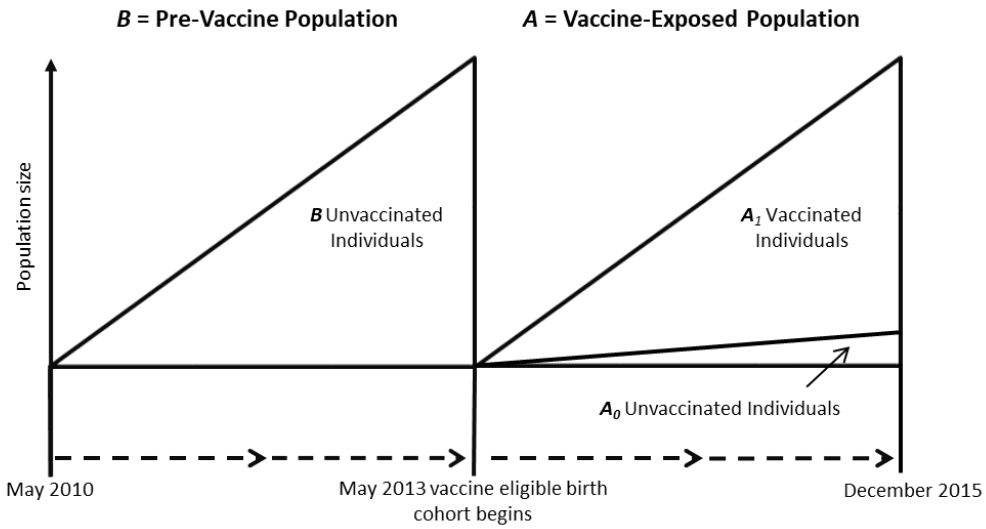

Figure 7-3 Population cohort groups for this study [*A* and *B* are separate in time.]

Cohort characteristics were compared between children from the pre- and post-vaccine periods. Continuous variables were tested by Student's *t*-test or Wilcoxon rank-sum test if not normally distributed and χ^2-test or Fisher's exact-test for categorical variables. All data analyses were performed using R Version 3.1.2 (224).

7.4.2 Method Two: alternative VE estimation

Selection of comparator populations using vaccination-propensity adjustment

Using population *A* where vaccination uptake is known, we generated a PS for the predicted probability of vaccine uptake based on known associations. Vaccine uptake with any dose was the binomial outcome variable, and registered GP practice and LSOA of residence were used as categorical predictors. These predictors were identified *a priori* based on the availability of data, previously unpublished local data analysis and published literature on risk factors for non-vaccination (20–24).

Often a PS is estimated using parametric model such as logistic regression model. Here we used a machine learning non-parametric regression model known as Generalised Boosting Model (GBM). A number of studies suggest GBM outperform PS estimation from simple logistic regression, providing a more flexible approach that may model nonlinear relationships using an iterative process with multiple regression trees (256,265). We used the "gbm" package in R to generate the PS (224,266). Although assessing PS performance with area under the receiver operator characteristic curve (AUC) or c-statistics is questionable,(267) in this study we used PS for predictive modelling rather than its traditional use. Therefore, using AUC was considered appropriate and a value of 0.87 indicated good predictive power.

We then applied the PS to population B, enabling B to be split into B_0which would have the lowest probability of being vaccinated (lower PS) if they were offered the rotavirus vaccine, and B_1 the highest probability of being vaccinated (Figure 7-4). The populations B_0 and B_1 were generated using a range of PSs including the 80th-90th-95th-99th percentiles for non-vaccination.

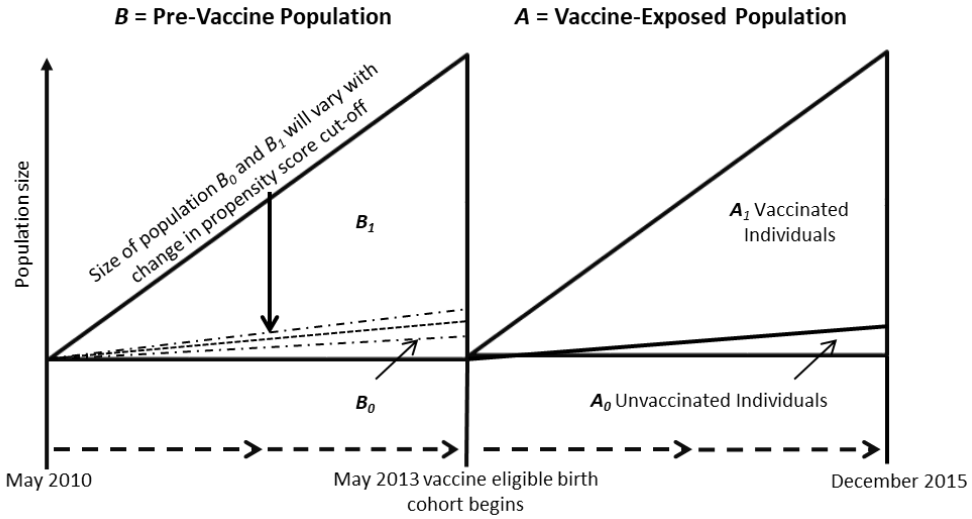

Figure 7-4 Conceptualised population cohort groups and sub-population comparators, utilising a vaccination-propensity adjustment for identification of population B_0

Estimating the indirect VE

An indirect VE can be estimated using a range of PSs to identify population B_0 (Figure 4) and can be written as

$$VE_{IDPS_x} = 1 - \frac{\lambda A_0(t)}{\lambda B_{0PS_x}(t)}$$

Abbreviations: VE, vaccine effectiveness; ID, indirect effect; PS, propensity score range for selecting the comparator population.

Because GP and residence information were used to generate the PS they could not be used for modelling VE. Therefore, a fixed-effects Cox regression model adjusting for gender and Index of Multiple Deprivation score was used to calculate VE for the indirect and total effects at a range of PS scores.

Estimating direct VE

Direct VE cannot be calculated robustly estimated using the comparator populations A_1 and A_0 because as discussed previously it is likely that differences in healthcare seeking behaviour between vaccinated (A_1) and unvaccinated groups (A_0) could cause substantial confounding. We therefore established the following mathematical formula for calculating direct VE.

Overall disease averted (O_{DA}) is a composite of the indirect and direct effect on three different populations: 1) those that are vaccinated (V) and receive a direct effect of vaccination; 2) those that have been vaccinated but in whom the vaccine has failed to exert a direct immune response / vaccine failures (Vf) but may still receive an indirect effect; 3) the unvaccinated population (UV) that may achieve an indirect effect through herd protection. The estimate of overall disease averted in a population can be written as:

$$\mathrm{O}_{DA} = \mathrm{V}_{DA} + Vf_{DA} + \mathrm{UV}_{DA}$$

Abbreviations: O_{DA}, overall disease averted by population vaccination; V_{DA}, disease averted in the vaccinated population; Vf_{DA}, disease averted in the population of vaccine failures; UV_{DA}, disease averted in the unvaccinated.

Components calculated by:

$$O_{DA} = VE_O \times P_A \times R$$

$$V_{DA} = VE_D \times R \times P_{A1}$$

$$Vf_{DA} = VE_{ID} \times R \times (P_{A1} \times (1 - VE_D))$$

$$UV_{DA} = VE_{ID} \times R \times P_{A0}$$

Abbreviations: VE_D ,direct vaccine effectiveness; VE_{ID} , indirect vaccine effectiveness; P_A, cohort A population; P_{A1}, number vaccinated; P_{A0}number unvaccinated; *R*, rate of disease in the pre-vaccine era.

Full equation to estimate Overall disease averted:

$$VE_O \times P_A \times R$$

$$= (VE_D \times R \times P_{A1}) + VE_{ID} \times R \times \left(P_{A1} \times (1 - VE_D)\right) + (VE_{ID} \times R \times P_{A0})$$

Therefore the indirect VE and overall VE estimates can be used in a rearranged equation to produce direct VE estimate and can be written as:

$$VE_D = \frac{(VE_0 - VE_{ID})P_A}{P_{A1}(1 - VE_{ID})}$$

Once indirect VE estimates were produced for different comparator populations selected using PS at 80th-90th-95th-99th percentiles for non-vaccination we were able calculate direct VE. We also specified what values within this range of percentiles would be considered epidemiologically and biologically plausible in context of rotavirus vaccination in a childhood cohort. This was pre-specified using the following criteria:

- Indirect VE should not be higher than direct VE in a cohort of the same age.

- Indirect and direct VE should not be below zero.
- Direct and indirect VE cannot be higher than the overall VE (maximum value at the 95% Upper CI).

7.5 Results – method one

7.5.1 Characteristics of the cohort

Six of the seven NHS CCGs in Merseyside, agreed to participate in the study. Therefore, 232 GPs had the opportunity to participate, and of these 135 (58%) consented. There was no difference in the IMD score for GP practices participating and those that declined. Records on 54 548 children were extracted from participating GPs (Figure 7-5); approximately 0.1% of the total registered population could not be extracted due to patient confidentiality. We excluded 905 children that were born outside of Merseyside or were missing covariates (LSOA, Gender, GP); 8336 children who were <6 months of age; and 48 children from the post-vaccine cohort (A) that had either received a dose of rotavirus vaccine after 6 months of age or had an invalid vaccination date. This left 45,259 in the cohort, comprising 23,020 in the pre-vaccine period and 22,239 in the post-vaccine period. Of the children in the post-vaccine period 91% (20,289) had received one rotavirus vaccine dose and 84% (18,733) received two doses (Table 7-1). In the post-vaccine period, children who were unvaccinated were more likely to have been from a socioeconomically deprived household (A_0 vs A_1: P<0.001) and to have been older / in the cohort for longer (A_0 vs A_1: P<0.001). Unvaccinated children were more likely to be older because vaccine uptake levels took several months after introduction to reach steady state (259).

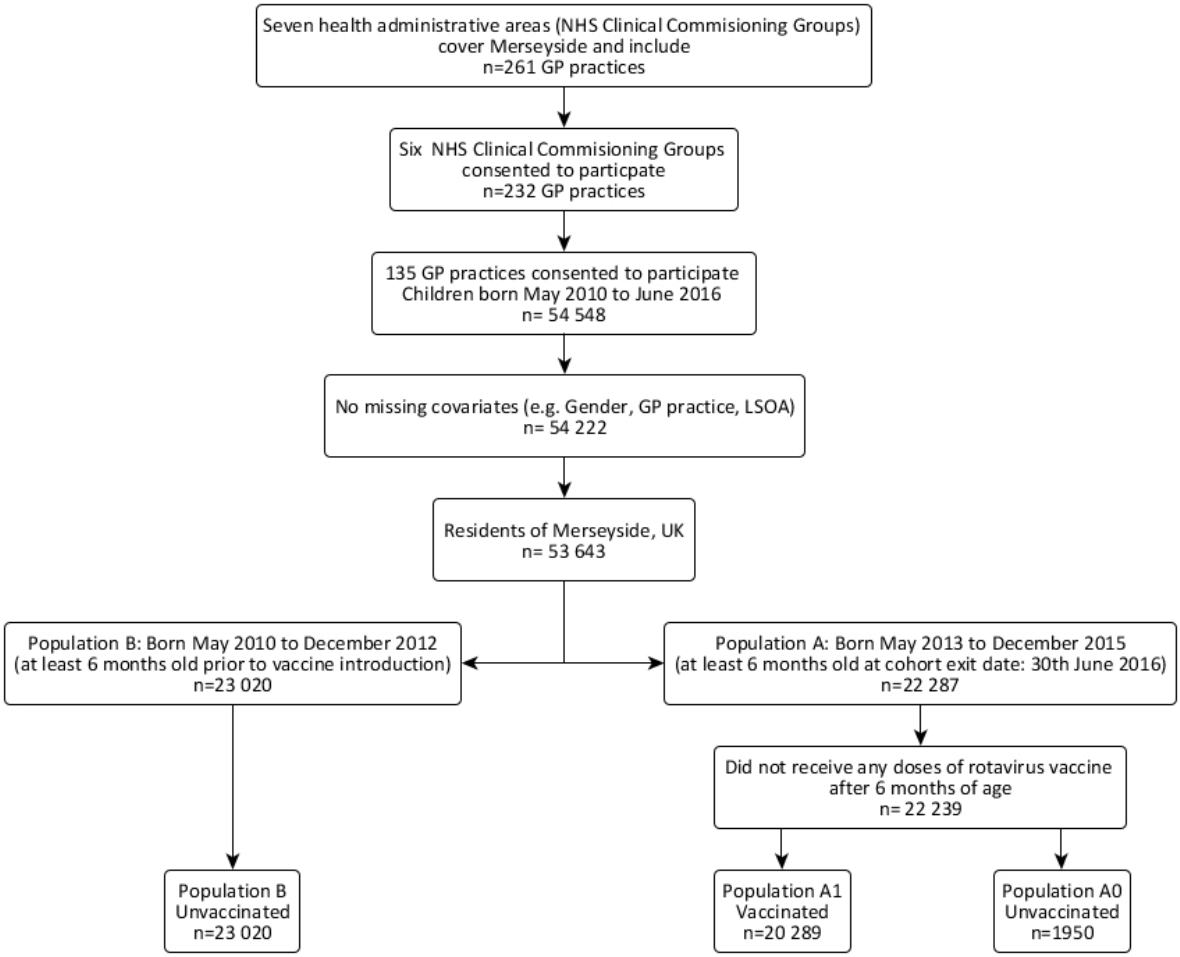

Figure 7-5 Study population.

[Abbreviations: NHS, National Health Service; GP, General Practice]

Table 7-1 Characteristics of the cohort Figures are n (%) (n=45,259)

Variable	Pre-vaccine period (B) (n=23020)	Post-vaccine period (A)			A_0 v A_1 (P value) †	B vs A (P value)†
		Vaccinated (A_1) (n=20289)	Unvaccinated (A_0) (n=1950)	Total (A) (n=22239)		
Male	11807 (51)	10489 (52)	1012 (52)	11501 (52)	0.866	0.371
Time in cohort (days)					<0.001	0.041
Median	412	412	504	412		
Lower quartile	177	170	261	182		
Upper quartile	685	682	777	685		
Number of vaccine doses						
0	23020 (100)	0	1950 (100)	1950 (9)	N/A	N/A
1	0	20289 (100)	0	20289 (91)		
2	0	18733 (92)	0	18733 (84)		
Index of Multiple Deprivation score					<0.001	0.001
Median	34.390	34.20	44.16	35.13		
Lower quartile	16.94	17.27	22.61	17.44		
Upper quartile	55.26	55.26	60.22	55.85		
Quintile of deprivation≠						
5 (least deprived)	1689 (7)	1381 (7)	79 (4)	1460 (7)	<0.001	0.014
4	2599 (11)	2313 (11)	154 (8)	2467 (11)		
3	3567 (15)	3261 (15)	241 (12)	3502 (16)		
2	3499 (15)	3065 (15)	279 (14)	3344 (15)		
1 (most deprived)	11666 (51)	10269 (51)	1197 (61)	11466 (52)		

† χ2-test and Wilcoxon rank-sum test

≠ Index of Multiple Deprivation score divided into quintiles

7.5.2 Direct, indirect, total and overall vaccine effectiveness

The overall VE ($A\ vs\ B$) for one or more doses of RV1 for preventing GP consultations for acute gastroenteritis and its symptoms in this cohort was 11% (95% CI 7%, 16%) (Table 7-2). If only time and events in-season (January to May) were

included overall VE ($A\ vs\ B$) increased to 30% (95% CI 25%, 34%). Using comparator populations specified in Method One the direct VE ($A_1\ vs\ A_0$) in our cohort was -46% (95% CI -70%, -26%). The indirect effect ($A_0\ vs\ B$) was 34% (95% CI 23%, 43%) and the total effect ($A_1\ vs\ B$) 9% (95% CI 4%, 14%). Similar to overall VE in-season, the direct, indirect and total effects were all higher in the rotavirus season (Table 7-2).

Table 7-2. Rotavirus vaccine effectiveness estimates against GP consultations for acute gastroenteritis: Method One

	Time period	1 or more doses vaccinated (A_1) n		Unvaccinated (A_0) n		Pre-vaccine population (B) n		Vaccine effectiveness (95% CI)
		Events	Population	Events	Population	Events	Population	
Direct	Full year	2632	20289	191	1950	-	-	-46 (-70,26)
	Jan-May	1362	19653	109	1913	-	-	-30 (-58,6)
Indirect	Full year	-	-	191	1950	3287	23020	34 (23,43)
	Jan-May	-	-	109	1913	2146	22308	41 (28,51)
Total	Full year	2632	20289	-	-	3287	23020	9 (4,14)
	Jan-May	1362	19653	-	-	2146	22308	29 (24,33)
Overall	Full year	2632	20289	191	1950	3287	23020	11 (7,16)
	Jan-May	1362	19653	109	1913	2146	22308	30 (25,34)

Abbreviations: CI, confidence interval.

7.6 Results - method two

Figure 7-6 presents the indirect and direct VE for a range of comparator populations selected using the PS; they are presented as 1-PS with percentiles towards non-vaccination. The 95th percentile fell at $1 - PS \geq 0.32$ (population B_0: n=1,008) giving an indirect vaccine effect of 2% and an associated direct effect of 10%; at the 99th percentile population where $1 - PS \geq 0.52$ the population size of B_0 was very low (n=164) and gave an indirect vaccine effect of 25% and direct effect of -21%.

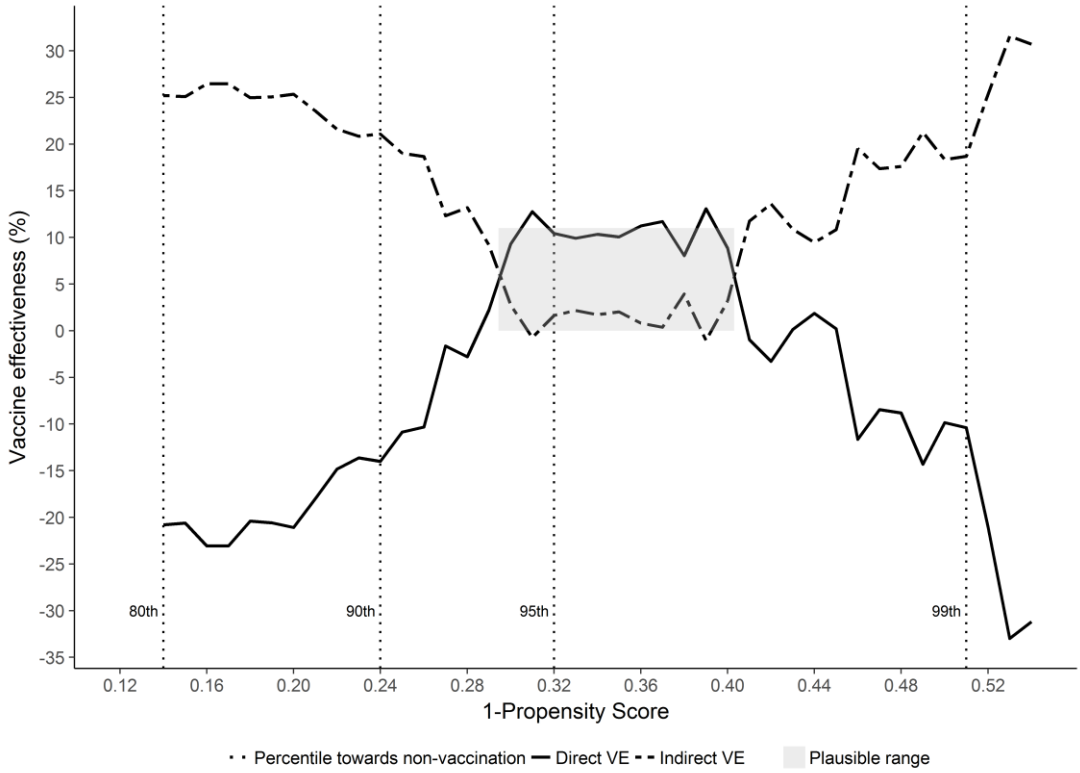

Figure 7-6. Indirect and direct vaccine effectiveness against GP consultations for acute gastroenteritis; for a range of comparator populations selected through vaccination-propensity adjustment [The values on the x axis include populations ≥ $\mathbf{1} - \boldsymbol{PS}$. The grey box represents a plausible range of values given prior knowledge of rotavirus and the vaccine. Abbreviations: VE, vaccine effectiveness]

The 95th percentile for non-vaccination fell within a range of values which were plausible. Following the specified criteria, plausible estimates for direct VE ranged from 8-11% and the indirect VE ranged from 0-4%

We also estimated indirect and direct VE for the rotavirus season only. Figure 7-7 shows the indirect and direct effects for in-season (January to May). At the 95th percentile indirect VE was 8% and direct VE 26% (population B_0: n=982), whereas at the 99th CI the indirect VE estimate was 38% giving a direct VE of -14% (population B_0: n=194). Within the plausible range of estimates (grey box), the

direct VE was calculated at between 17% and 29% for indirect VE estimated at between 5% and 17%.

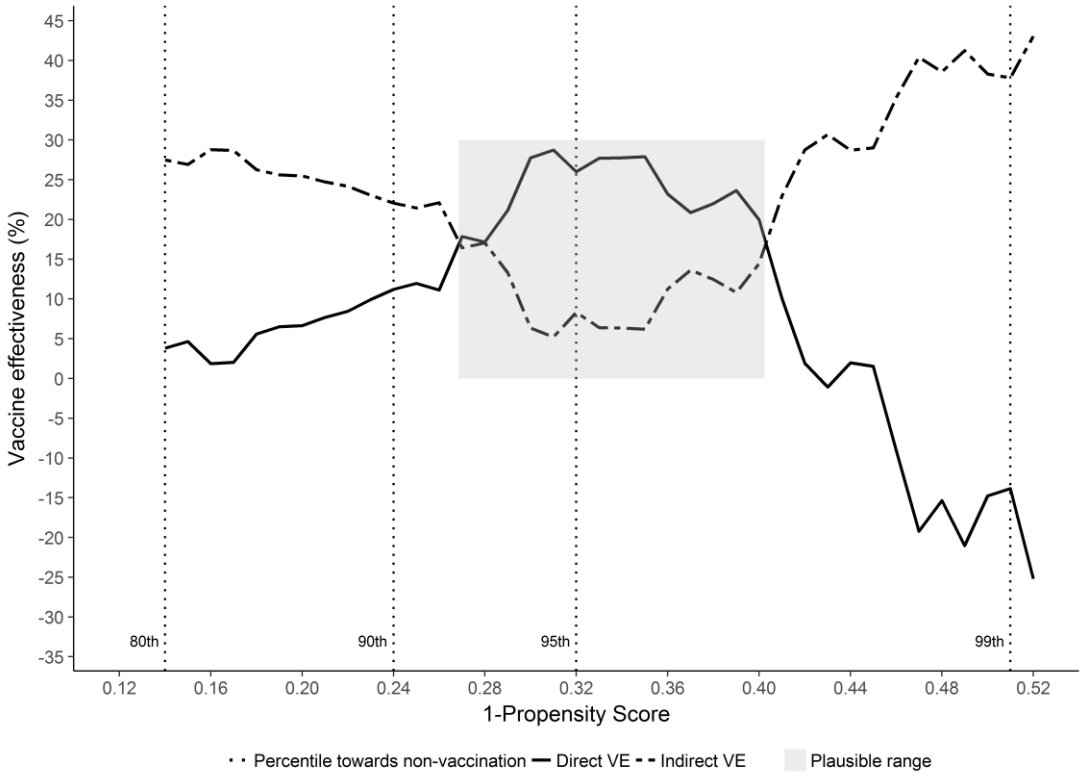

Figure 7-7 Indirect and direct vaccine effectiveness against GP consultations for acute gastroenteritis during the rotavirus season, for a range of comparator populations selected through vaccination-propensity adjustment (January to May) [The values on the x axis include populations $\geq 1 - PS$. The grey box represents a plausible range of values given prior knowledge of rotavirus and the vaccine. Abbreviations: VE, vaccine effectiveness]

7.7 Discussion

We have presented two methods for calculating direct and indirect VE in observational studies. The first, established method (Method One) is commonly cited in the literature for measurement of rotavirus vaccine impact and effectiveness (77,85,251). However, in order to provide accurate VE estimates it requires a study design with little to no bias and rigorous control over study participants that is often not afforded in effectiveness studies. The second methodology (Method Two)

attempts to mitigate for design limitations such as selection bias and confounding via the use of PS analysis.

Regardless of the two methods used, overall VE was estimated as 11% (95% CI 7%, 16%). When analysis was restricted to rotavirus season, thereby increasing specificity, the overall VE increased substantially to 30% (95% CI 25%, 34%). The overall estimates of VE compare well to those from the ecological study of the same population which used an interrupted time-series approach for analysis (Chapter 6). Thus rotavirus vaccination appears to be effective at reducing attendances to GPs, supporting findings from other studies assessing rotavirus VE against community attendances for acute gastroenteritis (174,175,177).

When estimating the components of overall VE, Method One produced estimates for direct (-46%) and indirect (34%) VE that were implausible, suggesting confounding, typical for this type of study design. For instance, the outcome measure depends on comparable healthcare seeking behaviour for each comparator group. However, by definition, those in the post-vaccine introduction vaccinated group (A_1) are more likely to access healthcare than the unvaccinated. Therefore, for mild disease which is more likely to be seen by GPs than at hospitals it may be assumed that the vaccinated (A_1) are more likely to seek healthcare contact when ill than the unvaccinated (A_0), resulting in a negative direct VE. This issue is also true of the pre-vaccine introduction cohort (B) using Method One, as this group will include persons that would either have been vaccinated or unvaccinated had rotavirus vaccine been available. Therefore under Method One a large positive indirect VE could be expected if direct VE is negative and the comparator population B is more likely to access healthcare than population A_0.

Method Two attempts to control for the confounding and bias in healthcare seeking behaviour by using a PS score to balance comparator populations. Method Two provided a range of direct (8% to 11%) and indirect VE (0 to 4%) estimates which are plausible given logical criteria based on epidemiological and biological knowledge of rotavirus disease and vaccination. Whilst point estimates of direct and indirect VE are difficult to specify using this method because they depend on selection of the most representative comparator populations, estimates at the 95th percentile were plausible for both full year and in-season VE estimates. Estimates at the 99th percentile were implausible and were generated using a very small comparator population for B_0. We opted not to calculate total VE in Method Two because of its limited public health relevance relative to the overall VE and because it is a composite of the direct and indirect effects.

To put our findings into context, a longitudinal cohort study conducted in the UK prior to rotavirus vaccine introduction identified rotavirus in 14% of stool samples obtained from children under five attending GP practices with infectious intestinal disease, with this figure likely to be higher in children under 2 years of age, and during the season when rotavirus activity is higher (36,227,245). Given the direct effects (8-11%) reported from Method Two and assuming rotavirus was the causative agent in 14% of gastroenteritis cases this would suggest an efficacy of between 57% and 78%. This is lower than that reported for severe disease in developed countries, but the cases in this cohort are likely to represent mild or moderate disease against which rotavirus vaccines are less efficacious (203,67).

This study was subject to limitations which are often associated with secondary routine healthcare data. We needed to consider the potential for clinical coding to lead to misclassification of disease, and this misclassification may vary by different

GP practice. We tried to account for any GP level effect through mixed effects models with GP practice as a random effect. We also investigated any temporal changes in coding with the NHS CCGs and there had been no recorded changes in practice during the dates of interest.

There are number of considerations and assumptions required for Method Two to be successful. Firstly, it requires data such as population level parameters or individual level characteristics for the generation of the PS. In this study using healthcare data from a clinical database, we had access to few individual and population level indicators. However, even with this level of data we were able to generate a PS with excellent discrimination based on a strong association between the covariates and the exposure (AUC=0.87). In order to utilise this method in other studies it is imperative that individual and population characteristics which are associated with exposure are available. However, in generating a PS the complexity of any covariates included need to be balanced with the need to keep the PS generalisable to the population. A trade-off between specificity and sensitivity is required. Secondly, applying a PS to population B requires an assumption that the populations A and B are comparable in the variables used to generate the propensity score. This assumption was appropriate in this study as we compared the same population at two periods that were temporally not too distant. Finally, the criteria used to identify the plausible range in this study are specific to the population and pathogen. Nonetheless, provided that indirect VE is measured in the same sub-set of the population as the direct VE, the criteria are likely to be applicable to rotavirus vaccination in other settings and pathogens with similar infectious disease dynamics, such as, short carriage and rapid acute symptoms. However, these criteria would be inappropriate for measuring indirect VE in sub-populations which are ineligible for vaccination but have high

incidence of disease, for example, the indirect effect of vaccination of children with Pneumococcal Conjugate Vaccine on Incidence of pneumococcal disease in older adults, where indirect may exceed direct VE (268).

In summary, although Method Two will not remove the temporal bias of ecological studies, it does provide a robust solution to dealing with selection bias caused by differences in healthcare access and health- seeking behaviour between vaccinated and unvaccinated groups. The method is particularly applicable to vaccine effectiveness studies using routine health data that wish to measure the broader public health impact of a vaccine through the use of non-pathogen specific syndromic endpoints. We envisage that this method will be immediately applicable to respiratory diseases such as influenza where there are multiple non-pathogen specific syndromic outcomes from influenza infection.

8 Summary, recommendations and further research

8.1 What this thesis adds to the knowledge base

I have used routine health data for a defined population to evaluate the effect of rotavirus vaccination on a range of health outcomes. To achieve this aim a series of inter-linked studies / analyses were conducted using ecological and cohort study designs. The effect of vaccination on gastrointestinal disease presentations at primary and secondary care in relation to vaccine uptake and deprivation has been described.

In the studies that make up this thesis a number of novel findings were identified. Whilst the impact of rotavirus vaccination on severe disease outcomes in high income countries has been well described, the impact across an entire healthcare economy for a defined population has not been described before. Importantly in vaccine eligible children, impact was shown across all outcome measures, in primary care and secondary care. The level of impact varied depending on the setting and the specificity of the outcome definition but was comparable with other studies conducted in high income settings.

In Merseyside uptake of rotavirus vaccine reached over 90% rapidly mirroring national trends (226). Like other routine childhood vaccines, uptake was not equitable across deprivation strata. First dose vaccine uptake and completion of the full dose schedule was significantly lower in the most socioeconomically deprived populations compared to the least deprived. Findings from this Merseyside based study also supported that of Pockett et al, 2011, that those living in the most deprived populations had the highest baseline incidence of all-cause acute gastroenteritis (AGE) admissions (159). These findings suggest that the most

deprived populations have the most to gain from rotavirus vaccination. Indeed this study shows that infants from the socioeconomically deprived populations derived the greatest benefit from rotavirus vaccination despite lower vaccine uptake. This is the first time an ecological study design has described rotavirus vaccine impact in relation to socioeconomic deprivation in a high income country.

The impact of vaccination on milder disease across all-age groups is underrepresented in the literature (240). This study presents evidence that in children <2 years of age where the burden of rotavirus disease is highest, vaccination is having a substantial impact on healthcare attendances for mild disease. Furthermore, results indicate that herd protection is also reducing mild disease in older adult populations, likely through the reduced transmission of rotavirus from children. This is an important finding as the majority of rotavirus related disease in healthy adults is likely to be mild and either result in home care or contact with primary care.

The novelty of measuring vaccine impact across primary and secondary care in parallel in a defined population provides robustness that any detected changes are due to rotavirus vaccination rather than the peculiarities of one particular data source. The delayed peak of rotavirus in 2-4 year olds in season two (2014/15) post-vaccine introduction detected nationally, in rotavirus laboratory detections and locally, at Alder Hey Children's NHS Foundation Trust was detected across all study outcome measures, strengthening the evidence that the datasets used in this study were useful in detecting rotavirus gastroenteritis for non-specific outcomes. These findings could potentially provide confidence for using similar datasets for other regional vaccine evaluation studies. However, the use of an ecological study design with multiple non-specific endpoints still means that we can still only infer vaccine impact and cannot prove a causal link. The reduction in rotavirus and non-specific AGE

outcomes could be related to unmeasured population changes, virus variance and environmental factors such as: changes to birth rates (affecting the number of immunological naïve susceptible infants); climate; and / or natural shifts in rotavirus genotype distribution. Although, these factors cannot be ruled out, they seem unlikely to be causing the significant reductions reported in this thesis. Particularly since, birth rates in Merseyside have stayed constant (230) and seasonal rotavirus genotype distributions in the UK pre-vaccine introduction were stable for decades (36,269–271).

The retrospective general practice (GP) birth cohort using routine data from primary care was an original approach to measuring rotavirus vaccine effectiveness (VE) against GP consultations for infectious gastroenteritis. This study was intended to allow a methodologically rigorous analysis of individual level rotavirus vaccine VE against milder non-specific disease. However, there were a number of issues with confounding associated with the use of a retrospective healthcare database. Therefore, these issues necessitated the development of a new methodology for designing and analysing VE in studies suffering from confounding, related to healthcare access / health-seeking behaviour. Use of an adaptive study designs, like that used here, are gaining prominence in case-control, cohort and ecological studies measuring VE and impact, as epidemiologists continually look to reduce study bias, maintain generalisability and ethics, whilst conducting cost-realistic studies (254,272). This methodology should therefore be useful to epidemiologists assessing the effect of interventions; specifically VE studies measuring multiple non-pathogen specific syndromic outcome. However, it requires application under different conditions, such as vaccines with lower vaccine uptake, (e.g influenza vaccine) to assess the generalisability of this method.

8.2 Recommendations arising from thesis

8.2.1 Data access and quality

As the studies included in this thesis were entirely based on analysis of routine health data, there has been the opportunity to assess the accessibility and usefulness of these data sources for infectious disease epidemiological research. Access to data is incredibly complex and time consuming, largely due to the complexities of NHS organisational structures across multiple local authorities (Figure 8-1).

There are aspects of this study that require improvement, firstly, there were substantial inconsistencies in clinical / symptomatic coding across services which provide similar if not identical functions but are commissioned by different organisations. For instance Read Codes, accident and emergency NHS codes or free-text were used by walk-in-centres (WIC) across Merseyside to record a patient's symptoms / clinical presentation. Secondly, there has been multiple instances of the organisations responsible for commissioning services not having access to full datasets for the services they commission, either because of restrictions in access caused by IT data provider contracts, organisation restructure or gaps in staff training. These experiences have led to the following specific recommendations:

- Data for this study came from multiple NHS organisations and was provided to the study team without financial remuneration. Access was only possible if NHS organisations could see the value of the study. The success of this study has therefore largely been facilitated by strong partnership working between the research team and partner agencies and a commitment to using an evidenced-based approach. Therefore identifying key individuals and fostering strong relationships early on in study design is crucial for a successful study.

- Regular contact with data providers including sites visits by researchers to observe data input and database storage is critical to understanding the complexities and idiosyncrasies of secondary clinical data. This effort will help to minimise study bias and the potential of erroneous findings.
- For anonymous data research / surveillance GPs and NHS CCGs should consider employing an opt out method for data sharing between GPs and NHS CCGs. NHS CCGs should act as the data custodian on behalf of GPs.
- IT systems procured for use by healthcare providers, should allow compatibility with legacy systems. Contracts with IT providers should not include costs for data access incurred by providers and commissioners.
- All anonymous data collected within the NHS on patients should be freely accessible to the organisations that commission the service in question and to the service providers.
- Permissions for data sharing for research purposes could be streamlined if multiple NHS Trusts and CCGs utilised a cross-organisation team for research governance and data protection.
- Study investigators should organise a regional event to feedback research finding and recommendations. Those invited should include: NHS Trusts; NHS CCGs; Public Health Departments at local authorities; Regional Public Health England; and NHS England Screening and Immunisation team. Lay members of these organisations should be invited. The event should also provide an opportunity for sharing future research priorities.

In the longer term many of the specific recommendations above would be redundant in secondary data studies if primary, secondary and community health data were linked as routine practice to create an anonymised unique record for each GP

registered patient. Access could then be governed on a study specific basis by the NHS Health Research Authority Confidentiality Advisory Group (CAG) (273).

8.2.2 Research design and analysis

The rotavirus vaccine programme was introduced universally across the UK in July 2013, therefore population-level vaccine impact studies have been limited to a cohort or time-series design with 'before and after' comparator populations. The use of more robust pragmatic study designs and analysis could be utilised for this and other vaccines. For example, although not feasible for evaluating rotavirus vaccination in the UK, a cluster randomised stepped wedge design could be both politically, analytically and logistically appealing for a new vaccine programme (109,274). Alternatively, novel analytical methods could be used to minimise unmeasured bias and confounding, helping to disentangle changes in outcome measures that are related to the vaccine and changes that are caused by extraneous factors. In this thesis propensity score analysis was utilised in an original methodology to balance comparator populations in a birth cohort through minimising confounding related to healthcare seeking behaviour. Other methodologies may also have been applicable and may warrant investigation for future analyses. One such method uses synthetic controls for adjusting interrupted time-series models (272,275). In this approach multiple control time-series are weighted based on their fit to the pre-vaccine introduction time-series of the outcome of interest and combined into one control time-series. Unmeasured bias and confounding is effectively adjusted for, using the synthetic control's predicted counterfactual estimates of what would have occurred in the post-intervention period if the vaccine had not been introduced (272).

8.2.3 Microbiology standards

The significant reduction in laboratory confirmed rotavirus at Alder Hey Children's NHS Foundation Trust and mirrored at other acute hospitals may encourage rotavirus diagnostic and genotypic testing practices to change. The decrease in RVGE is likely to mean the relative prevalence of other AGE causing pathogens, such as norovirus and adenovirus increases. It may be sensible and cost-effective for paediatric hospitals to begin testing for these pathogens if not already doing so. However, as it is only four years since rotavirus vaccine introduction, routine paediatric testing should continue, so that the long term effect of vaccination on paediatric RVGE epidemiology can be monitored, especially genotype distributions and prevalence.

8.2.4 Vaccine policy

Finally, the findings that vaccination in the most socioeconomically deprived communities has the largest impact on population disease burden despite lower vaccine uptake, further highlights the need for additional targeted immunisation campaigns in socioeconomically deprived populations to maximise vaccine impact and cost-effectiveness. Whilst identifying deprived areas at the micro-population level is relatively straightforward, understanding the enablers and barriers for vaccination in these communities is challenging; particularly since opinions are fluid. However, successfully increasing uptake of routine childhood vaccinations in the most deprived areas will contribute to reducing health inequalities and help "give each child the best start in life" (276,277).

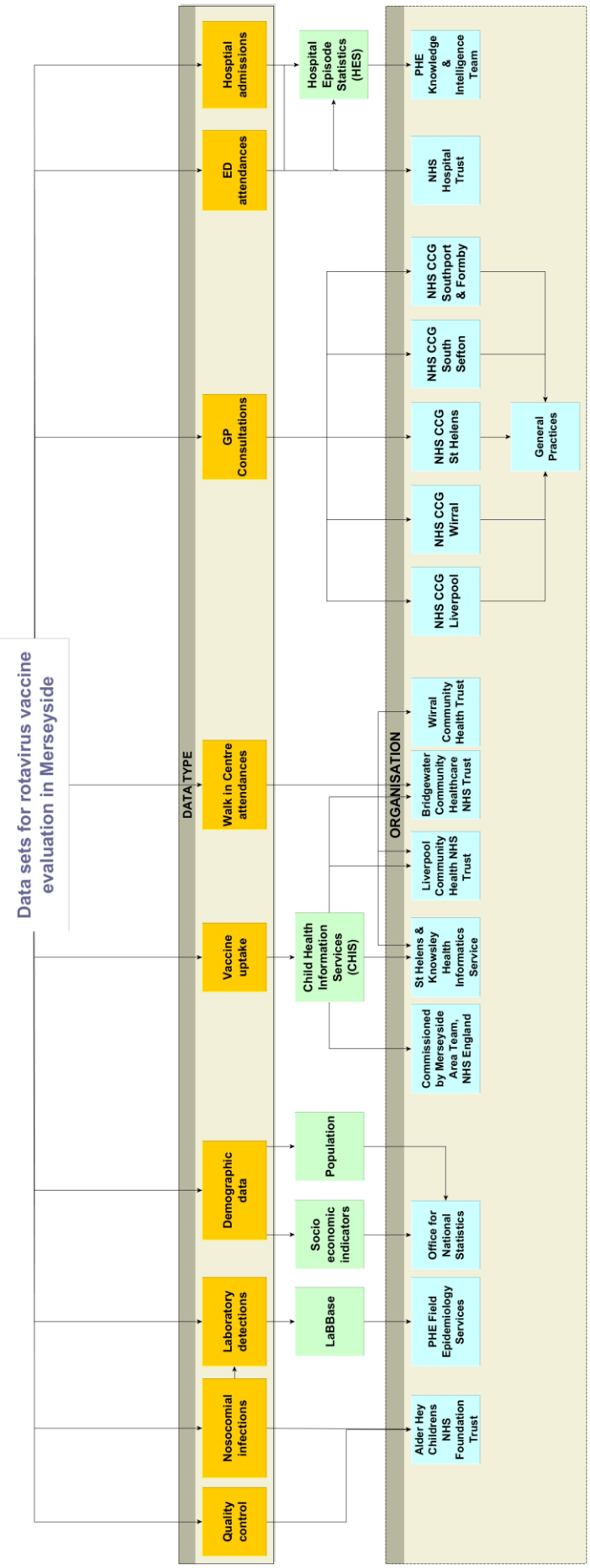

Figure 8-1 End of study schematic of data sources and providers across Merseyside

8.3 Further research

This study was conducted over only 3 years post-vaccine introduction on routine health data. Whilst there is strong evidence that rotavirus vaccination has significantly reduced healthcare use for AGE across both primary and secondary care, in vaccine eligible infants, and young children, the long-term impact of vaccination on these cohorts is as yet uncertain. Prior to vaccination in the UK, there was a well-defined rotavirus season occurring between January and May each year with peak incidence in late March (36). Infections were predominately caused by the G1P[8] genotype (56%) and ~90% of RVGE was in children less than 5 years old. However, persons aged 5 years and over were more likely to be infected with non-G1P[8] genotypes. Odds of infection with less common non-G1P[8] strains also increased out of rotavirus season (June-December), as did the odds of infection in persons aged 5 years and over. This pattern of a relative proportional increase in less common genotypes out-of-season and the associated reduction in rotavirus incidence are reflected in countries which have introduced vaccination (278,279). Furthermore, since vaccine introduction there is the potential that vaccinated children will have reduced exposure to both natural primary and secondary infections as a child because they are only being exposed to G1P[8] in the Rotarix® vaccine. Therefore, further work should explore the hypothesis that heterotypic immunity to non-G1P[8] genotypes in the vaccinated cohort will be lower than in the pre-vaccine era, leaving this cohort more susceptible to heterotypic infections as older children and adults, potentially increasing the risk of outbreaks in older children.

To achieve these aims, serological data, cohort healthcare data from hospitals and primary care and mathematical models would be required to predict how routine childhood vaccination may alter the epidemiology of rotavirus infection. Specifically,

looking to investigate how rotavirus genotype distribution and risk of rotavirus infection changes as a vaccinated cohort ages. Then to validate the model predictions against routinely collected epidemiological data. Any changes to disease patterns will have implications for diagnostics, outbreak prevention and response and the public impact and societal cost. This study would therefore be important and unique; integrating detailed serology, genotyping and incidence data into mathematical models will allow us to understand, monitor and predict any changes in the epidemiology of rotavirus infections. This work would support vaccine programme policy and health protection preparedness going forward.

It was not possible within the scope of this study to determine the economic cost of rotavirus ‘before and after’ vaccine introduction across a healthcare system in relation to socioeconomic deprivation and vaccine uptake. Economic evaluations of the impact of rotavirus vaccine exist but have mainly focussed on the effect on severe disease presentations and specific endpoints. What is lacking is an economic assessment of the impact on the wider healthcare system, taking into account less specific endpoints and societal costs. However, the data collected in this study along with previously published data could be used to parameterise an economic-cost model for direct medical and indirect patient / carer costs associated with an episode of acute viral gastroenteritis. For instance, these data would allow the medical costs of an episode to be extrapolated from resources such as the Unit Costs of Health and Social Care and the NHS reference costs (280,281). Whereas the indirect patient / carer costs could be estimated using data from the previously published Infectious Intestinal Diseases Study (IID2), UK. A cost saving per episode and a total cost saving could then be calculated, which can be further analysed for differential impact across socioeconomic strata.

In addition to the commonly associated symptoms of diarrhoea and vomiting, rotavirus infection is associated with childhood seizures. Prior to vaccine introduction, a large multi-centre study in Canada, showed that 7% of children hospitalised with laboratory confirmed rotavirus infection had seizures (282). Rotavirus vaccine introduction in the United States has been associated with a 18-21% reduction in emergency department or hospital diagnosed seizures (283). In Australia there has been a 35-38% reduction in febrile seizure hospitalisations in children under 2 years of age, since rotavirus vaccine introduction.

As yet, no study has been conducted in the UK to assess the population impact of rotavirus vaccination on afebrile and febrile seizures. However, preliminary analysis by this research team suggest a 34% reduction in hospitalisations for all-cause AGE with a co-diagnosis of febrile seizure in children under 5 years of age since introduction of rotavirus vaccination. Therefore an ecological study to assess the impact of rotavirus vaccination in children under 5 years of age on seizure hospitalisations; and, to estimate the unmeasured incidence of seizures associated with rotavirus infection would be welcome.

In this thesis a novel method for dealing with bias in observational vaccine effectiveness studies is described and tested using rotavirus vaccination in a GP birth cohort. However, it is now necessary to test the applicability of the novel method in other relevant studies. An adapted application of the methodology is planned for investigating the impact of pneumococcal conjugate and rotavirus vaccine over time in Malawi, using all-cause mortality as the outcome and population level demographic survey data for reducing confounding through balancing comparator groups (284).

Lastly, ongoing work is required to understand the underlying barriers and enablers to childhood vaccine uptake in socioeconomically deprived communities. The evidence included in this thesis has already supported a public engagement grant for understanding attitudes to vaccination in the Liverpool community and is supporting ongoing work to develop educational resources through an iterative process in the community.

8.4 Conclusions

In summary, this thesis has presented a wide body of evidence that rotavirus vaccination reduced healthcare use related to AGE, in young children in a defined geographic area; ranging from rotavirus specific hospitalisations to milder disease presenting to GPs and WICs. Furthermore, there is also indication that vaccination is offering herd protection particularly to older adults. The findings also offer evidence that rotavirus vaccination reduces severe disease burden in the most socioeconomically deprived populations, despite lower vaccine uptake. These data should support national measures to reduce health inequalities by improving vaccine uptake in the most deprived communities. Lastly, in the process of assessing rotavirus VE in primary care a novel methodology was developed to mitigate the often inherent bias in routine health data. This method will be particularly applicable to clinicians, epidemiologists and public health professionals that wish to measure the wider public health impact of a vaccine through syndromic endpoints in routine healthcare data.

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Appendix A: Supporting manuscripts

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BMC Infectious Diseases

RESEARCH ARTICLE Open Access

Population effectiveness of the pentavalent and monovalent rotavirus vaccines: a systematic review and meta-analysis of observational studies

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Abstract

Background: Rotavirus was the leading cause of acute gastroenteritis (AGE) in infants and young children prior to the introduction of routine vaccination. Since 2006 there have been two licensed vaccines available; with successful clinical trials leading the World Health Organization to recommend rotavirus vaccination for all children worldwide. In order to inform immunisation policy we have conducted a systematic review and meta-analysis of observation studies to assess population effectiveness against acute gastroenteritis.

Methods: We systematically searched PubMed, Medline, Web of Science, Cinhal and Academic Search Premier and grey literature sources for studies published between January 2006 and April 2014. Studies were eligible for inclusion if they were observational measuring population effectiveness of rotavirus vaccination against health care attendances for rotavirus gastroenteritis or AGE. To evaluate study quality we use used the Newcastle-Ottawa Scale for non-randomised studies, categorising studies by risk of bias. Publication bias was assessed using funnel plots. If two or more studies reported a measure of vaccine effectiveness (VE), we conducted a random effects meta-analysis. We stratified analyses by World Bank country income level and used study quality in sensitivity analyses.

Results: We identified 30 studies, 19 were from high-income countries and 11 from middle-income countries. Vaccine effectiveness against hospitalization for laboratory confirmed rotavirus gastroenteritis was highest in high-income countries (89% VE; 95% CI 84-92%) compared to middle-income countries (74% VE; 95% CI 67-80%). Vaccine effectiveness was higher for those receiving the complete vaccine schedule (81% VE; 95% CI 75-86%) compared to partial schedule (62% VE; 95% CI 55-69%). Two studies from high-income countries measured VE against community consultations for AGE with a pooled estimate of 40% (95% CI 13-58%; 2 studies).

Conclusions: We found strong evidence to further support the continued use of rotavirus vaccines. Vaccine effectiveness was similar to that reported in clinical trials for both high and middle-income countries. There is limited data from Low income settings at present. There was lower effectiveness against milder disease. Further studies, should continue to report effectiveness against AGE and less-severe rotavirus disease because as evidenced by pre-vaccine introduction studies this is likely to contribute the greatest burden on healthcare resources, particularly in high-income countries.

Keyword: Rotavirus, Vaccine effectiveness, Gastroenteritis, Meta-Analysis, Systematic review

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Open Access Protocol

BMJ Open

Ecological assessment of the direct and indirect effects of routine rotavirus vaccination in Merseyside, UK using data from multiple health systems: a study protocol

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ABSTRACT

Introduction: Rotavirus is the most common cause of severe gastroenteritis in infants and young children worldwide. Currently 67 countries include rotavirus vaccine in childhood immunisation programmes, but uptake in Western Europe has been slow. In July 2013, rotavirus vaccine was introduced into the UK's routine childhood immunisation programme. Prior to vaccine introduction in the UK, rotavirus was estimated to result in 750 000 diarrhoea episodes and 80 000 general practice (GP) consultations each year, together with 45% and 20% of hospital admissions and emergency department attendances for acute gastroenteritis, in children under 5 years of age. This paper describes a protocol for an ecological study that will assess rotavirus vaccine impact in the UK, to inform rotavirus immunisation policy in the UK and in other Western European countries.

Methods and analysis: In Merseyside, UK, we will conduct an ecological study using a 'before and after' approach to examine changes in gastroenteritis and rotavirus incidence following the introduction of rotavirus vaccination. Data will be collected on mortality, hospital admissions, nosocomial infection, emergency department attendances, GP consultations and community health consultations to capture all healthcare providers in the region. We will assess both the direct and indirect effects of the vaccine on the study population. Comparisons of outcome indicator rates will be made in relation to vaccine uptake and socioeconomic status.

Ethics and dissemination: The study has been approved by NHS Research Ethics Committee, South Central-Berkshire REC Reference: 14/SC/1140. Study outputs will be disseminated through scientific conferences and peer-reviewed publications. The study will demonstrate the impact of rotavirus vaccination on the burden of disease from a complete health system perspective. It will identify key areas that require improved data collection tools to maximise the usefulness of this surveillance approach and will provide a template for vaccine evaluations using ecological methods in the UK.

Strengths and limitations of this study

- Strengths include use of data from multiple health systems that will allow examination of the relative impact of vaccination on the various health providers and communities rather than the individual. These multiple data sources will provide robustness, enabling easier identification of outliers from overall trends.
- The study will include all ages for rotavirus and all-cause gastroenteritis incidence for 3 years postvaccination, thereby minimising confounding caused by yearly variance in rotavirus numbers.
- Additionally the study is powered to measure the indirect (herd) effect on hospital admissions, and while the majority of studies have focused on this, this study will also provide evidence for the indirect effect in emergency departments and community settings.
- The study will be limited by the ecological before and after design, and the difficulties of ascribing causality to vaccine, as well as the inherent risks of bias and confounding in observational studies particularly due to underlying secular trends.
- Use of syndromic indicators that are non-specific to rotavirus will limit the study to measuring large effects rather than small variations for emergency departments and community health outcome measures.

INTRODUCTION

Rotavirus is the most common cause of severe gastroenteritis in infants and young children, responsible for an estimated annual 453 000 deaths worldwide among children under age 5 years, with over 90% of deaths occurring in the developing countries.[1] In the UK, rotavirus gastroenteritis (RVGE) is seasonal and most cases occur between February and April each year. Rotavirus is estimated to result in 750 000 diarrhoea episodes and 80 000

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Short report

Early impact of rotavirus vaccination in a large paediatric hospital in the UK

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SUMMARY

The impact of routine rotavirus vaccination on community-acquired (CA) and healthcare-associated (HA) rotavirus gastroenteritis (RVGE) at a large paediatric hospital, UK, was investigated over a 13-year period. A total of 1644 hospitalized children aged 0–15 years tested positive for rotavirus between July 2002 and June 2015. Interrupted time-series analysis demonstrated that, post vaccine introduction (July 2013 to June 2015), CA- and HA-RVGE hospitalizations were 83% [95% confidence interval (CI): 72–90%) and 83% (95% CI: 66–92%] lower than expected, respectively. Rotavirus vaccination has rapidly reduced the hospital rotavirus disease burden among both CA- and HA-RVGE cases.

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Rotavirus vaccine impact and socioeconomic deprivation: an interrupted time-series analysis of gastrointestinal disease outcomes across primary and secondary care in the UK

Daniel Hungerford[1,2,3,4*], Roberto Vivancos[2,3,4], Jonathan M. Read[3,4,5], Miren Iturriza-Gómara[1,3], Neil French[1†] and Nigel A. Cunliffe[1,6†]

Abstract

Background: Rotavirus causes severe gastroenteritis in infants and young children worldwide. The UK introduced the monovalent rotavirus vaccine (Rotarix®) in July 2013. Vaccination is free of charge to parents, with two doses delivered at 8 and 12 weeks of age. We evaluated vaccine impact across a health system in relation to socioeconomic deprivation.

Methods: We used interrupted time-series analyses to assess changes in monthly health-care attendances in Merseyside, UK, for all ages, from July 2013 to June 2016, compared to predicted counterfactual attendances without vaccination spanning 3–11 years pre-vaccine. Outcome measures included laboratory-confirmed rotavirus gastroenteritis (RVGE) hospitalisations, acute gastroenteritis (AGE) hospitalisations, emergency department (ED) attendances for gastrointestinal conditions and consultations for infectious gastroenteritis at community walk-in centres (WIC) and general practices (GP). All analyses were stratified by age. Hospitalisations were additionally stratified by vaccine uptake and small-area-level socioeconomic deprivation.

Results: The uptake of the first and second doses of rotavirus vaccine was 91.4% (29,108/31,836) and 86.7% (27,594/31,836), respectively. Among children aged < 5 years, the incidence of gastrointestinal disease decreased across all outcomes post-vaccine introduction: 80% (95% confidence interval [CI] 70–87%; $p < 0.001$) for RVGE hospitalisation, 44% (95% CI 35–53%; $p < 0.001$) for AGE hospitalisations, 23% (95% CI 11–33%; $p < 0.001$) for ED, 32% (95% CI 7–50%; $p = 0.02$) for WIC and 13% (95% CI -3–26%; $p = 0.10$) for GP. The impact was greatest during the rotavirus season and for vaccine-eligible age groups. In adults aged 65+ years, AGE hospitalisations fell by 25% (95% CI 19–30%; $p < 0.001$). The pre-vaccine risk of AGE hospitalisation was highest in the most socioeconomically deprived communities (adjusted incident rate ratio 1.57; 95% CI 1.51–1.64; $p < 0.001$), as was the risk for non-vaccination (adjusted risk ratio 1.54; 95% CI 1.34–1.75; $p < 0.001$). The rate of AGE hospitalisations averted per 1,000 first doses of vaccine was higher among infants in the most deprived communities compared to the least deprived in 2014/15 (28; 95% CI 25–31 vs. 15; 95% CI 12–17) and in 2015/16 (26; 95% CI 23–30 vs. 13; 95% CI 11–16).

(Continued on next page)

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Appendix B: Ethical approvals

NHS
Health Research Authority

NRES Committee South Central - Berkshire

Bristol REC Centre
Whitefriars
Level 3, Block B
Lewins Mead
Bristol
BS1 2NT

Tel: 01173421390
Fax: 01173420445

12 December 2014

Professor Nigel Cunliffe
Professor
University of Liverpool
Institute of Infection and Global Health
The Ronald Ross Building
8 West Derby Street
L697BE

Dear Professor Cunliffe

Study title:	**Assessment of the effect of routine childhood rotavirus vaccination on a health system in Merseyside, UK**
REC reference:	**14/SC/1140**
Protocol number:	**UoL001057**
Amendment number:	**1**
Amendment date:	**18 November 2014**
IRAS project ID:	**155049**

The above amendment was reviewed by the Sub-Committee in correspondence.

Ethical opinion

The members of the Committee taking part in the review gave a favourable ethical opinion of the amendment on the basis described in the notice of amendment form and supporting documentation.

The sub-committee reviewed the following amendment;
1. Additional birth cohort analysis of GP data.

Approved documents

The documents reviewed and approved at the meeting were:

Document	*Version*	*Date*
Notice of Substantial Amendment (non-CTIMP)	1	18 November 2014
Research protocol or project proposal	3.0	01 November 2014

A Research Ethics Committee established by the Health Research Authority

Membership of the Committee

The members of the Committee who took part in the review are listed on the attached sheet.

R&D approval

All investigators and research collaborators in the NHS should notify the R&D office for the relevant NHS care organisation of this amendment and check whether it affects R&D approval of the research.

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

We are pleased to welcome researchers and R & D staff at our NRES committee members' training days – see details at http://www.hra.nhs.uk/hra-training/

14/SC/1140:	**Please quote this number on all correspondence**

Yours sincerely

Mr David Carpenter
Chair

E-mail: nrescommittee.southcentral-berkshire@nhs.net

Enclosures: *List of names and professions of members who took part in the review*

Copy to: *Mr Gavin Soady, Alder Hey Children's NHS Foundation Trust*
Mr Alex Astor

A Research Ethics Committee established by the Health Research Authority

NRES Committee South Central - Berkshire

Attendance at Sub-Committee of the REC meeting in correspondence

Committee Members:

Name	*Profession*	*Present*	*Notes*
Mr David Carpenter	Social Scientist	Yes	
Ms Susan Tonks	Senior Research Support Associate	Yes	

Also in attendance:

Name	*Position (or reason for attending)*
Ms Rae Granville	REC Manager

A Research Ethics Committee established by the Health Research Authority

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07 July 2014

Professor Nigel Cunliffe
Professor
University of Liverpool
Institute of Infection and Global Health
The Ronald Ross Building
8 West Derby Street
L697BE

Dear Professor Cunliffe

Study title:	**Assessment of the effect of routine childhood rotavirus vaccination on a health system in Merseyside, UK**
REC reference:	**14/SC/1140**
Protocol number:	**UoL001057**
IRAS project ID:	**155049**

The Proportionate Review Sub-committee of the NRES Committee South Central - Berkshire reviewed the above application on 03 July 2014.

We plan to publish your research summary wording for the above study on the NRES website, together with your contact details, unless you expressly withhold permission to do so. Publication will be no earlier than three months from the date of this favourable opinion letter. Should you wish to provide a substitute contact point, require further information, or wish to make a request to postpone publication, please contact the REC Manager Ms Rae Granville, nrescommittee.southcentral-berkshire@nhs.net.

Ethical opinion

On behalf of the Committee, the sub-committee gave a favourable ethical opinion of the above research on the basis described in the application form, protocol and supporting documentation, subject to the conditions specified below.

Conditions of the favourable opinion

The favourable opinion is subject to the following conditions being met prior to the start of the study.

Management permission or approval must be obtained from each host organisation prior to the start of the study at the site concerned.

Management permission ("R&D approval") should be sought from all NHS organisations involved in the study in accordance with NHS research governance arrangements.

Guidance on applying for NHS permission for research is available in the Integrated Research Application System or at http://www.rdforum.nhs.uk.

Where a NHS organisation's role in the study is limited to identifying and referring potential participants to research sites ("participant identification centre"), guidance should be sought from the R&D office on the information it requires to give permission for this activity.

For non-NHS sites, site management permission should be obtained in accordance with the procedures of the relevant host organisation.

Sponsors are not required to notify the Committee of approvals from host organisations.

Registration of Clinical Trials

All clinical trials (defined as the first four categories on the IRAS filter page) must be registered on a publically accessible database within 6 weeks of recruitment of the first participant (for medical device studies, within the timeline determined by the current registration and publication trees).

There is no requirement to separately notify the REC but you should do so at the earliest opportunity e.g. when submitting an amendment. We will audit the registration details as part of the annual progress reporting process.

To ensure transparency in research, we strongly recommend that all research is registered but for non-clinical trials this is not currently mandatory.

If a sponsor wishes to contest the need for registration they should contact Catherine Blewett (catherineblewett@nhs.net), the HRA does not, however, expect exceptions to be made. Guidance on where to register is provided within IRAS.

It is the responsibility of the sponsor to ensure that all the conditions are complied with before the start of the study or its initiation at a particular site (as applicable).

Ethical review of research sites

The favourable opinion applies to all NHS sites taking part in the study, subject to management permission being obtained from the NHS/HSC R&D office prior to the start of the study (see "Conditions of the favourable opinion").

Approved documents

The documents reviewed and approved were:

Document	*Version*	*Date*
Evidence of Sponsor insurance or indemnity (non NHS Sponsors only)		
Letter from sponsor		
REC Application Form [REC_Form_02072014]		02 July 2014
Referee's report or other scientific critique report		
Research protocol or project proposal	2.0	23 June 2014
Summary CV for Chief Investigator (CI)	1	07 January 2014
Summary, synopsis or diagram (flowchart) of protocol in non technical language	1	03 June 2014

Membership of the Proportionate Review Sub-Committee

The members of the Sub-Committee who took part in the review are listed on the attached sheet.

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

After ethical review

Reporting requirements

The attached document "After ethical review – guidance for researchers" gives detailed guidance on reporting requirements for studies with a favourable opinion, including:

- Notifying substantial amendments
- Adding new sites and investigators
- Notification of serious breaches of the protocol
- Progress and safety reports
- Notifying the end of the study

The HRA website also provides guidance on these topics, which is updated in the light of changes in reporting requirements or procedures.

Feedback

You are invited to give your view of the service that you have received from the National Research Ethics Service and the application procedure. If you wish to make your views known please use the feedback form available on the HRA website
http://www.hra.nhs.uk/about-the-hra/governance/quality-assurance/

We are pleased to welcome researchers and R & D staff at our NRES committee members' training days – see details at http://www.hra.nhs.uk/hra-training/

With the Committee's best wishes for the success of this project.

14/SC/1140	Please quote this number on all correspondence

Yours sincerely

Mr David Carpenter
Chair

Email: nrescommittee.southcentral-berkshire@nhs.net

Enclosures: *List of names and professions of members who took part in the review*

"After ethical review – guidance for researchers"

Copy to: *Mr Alex Astor*
Mr Gavin Soady, Alder Hey Children's NHS Foundation Trust

Appendix C: Supplementary tables

Table S1 study characteristics of seven cohort studies published between January 2006 and April 2014.

Study	Country	Vaccine introduction year	Vaccine coverage	Study period	Setting	Outcome	Cohort definition	Vaccine status	VE measure
Eberly et al. 2011	USA	2006	54%	July 2003-June 2009	Military health system database	Hospitalisation for RVGE	Cohort of all US military dependents <5 years enrolled in Department of Defence's health care program	Outpatient records contained within database	1-RR x 100 (crude)
Fontes-Vieira et al. 2011	Brazil	2006 (National immunisation programme)	NR	December 2006-December 2008	Monitored at home every 2 weeks	All-cause diarrhoea and RV (+) diarrhoea	Cohort of 500 children under 1 year. Reports cumulative incidence of all-cause diarrhoea and number of samples RV positive in vaccinated and unvaccinated groups.	Vaccination card and health centre databases	NR calculated by reviewers.
Muhsen et al. 2011	Israel	2007 (partial reimbursement offered)	55%	September 2008-January 2009	Health maintenance organisation (HMO) database	AGE requiring a physician visit in infants < 1 year (Physician diagnoses coded as AGE according to ICD 9)	Cohort of 34,642 infants analysed. Exposure variable: RV vaccine purchased before September 1st 2008	Vaccine purchases (HMO database)	1-RR x 100, stratified by number of doses purchased and socioeconomic status

Nolan et al. 2012	USA (Philadelphia)	2006	78.2% (1+) 65% (full)	Feb 2006 – Feb 2008	Electronic Health Record of a Paediatric Practice Based Research Network	AGE community consultation, AGE after hours telephone calls, or AGE episode (combination of calls and consultations occurring within 10 days of each other to estimate discrete episodes)	A total of 24,679 children eligible for RVV. Cohort 1 - children eligible in both 2007 & 2008 – 13951 (9351 received vaccine). Further divided in to 1a – 2007 season, and 1b 2008 season (mutually exclusive) Cohort 2 – children only eligible in 2008 – 10728 (9958 received vaccine).	Electronic Health Record	1-IRR x 100, adjusted for age at start of season, race, practice location, presence of a chronic condition, well child visits up to date, non-RV immunisations up to date, total sick-child visits, time in cohort.
Panozzo et al. 2014	USA	2006	51% in 2007 - 86% I n 2010	Born May 2000-April 2005 and born May 2006- April 2010	National Health Insurance Claims Database	ICD9 Codes identifying RVGE & AGE hospitalisations	Cohort of 905,718 children aged 8-20 months who had received at least 1 dose of DTaP.	Coding in National Health Insurance Claims Database	1-Hx100 Cox regression. Age was the time variable and analyses were stratified by year and adjusted for birth month.
Wang et al. 2010	USA	2006	NR	2007 & 2008 Rotavirus Seasons	National Health Insurance Claims Database	ICD10 Codes identifying RVGE & AGE outpatient consultations, hospitalisations and ED presentations. ED presentations and hospitalisations were combined into one outcome.	A total of 42306 infants who had received at least one dose of RV5 and a concurrent group of 28,417 infants who had not received RV5 but had received a first dose of DTaP.	Vaccination codes or National drug codes o health insurance claims.	VE = 1- rate ratio comparing infants receiving RV5 to DTaP. AGE outcomes were adjusted for gender and calendar year. RVGE outcomes not adjusted due to small numbers
Wang et al. 2013	USA	2006	NR	2007 & 2008 Rotavirus Seasons	National Health Insurance Claims Database	ICD10 Codes identifying RVGE & AGE outpatient consultations, hospitalisations and ED presentations. ED presentations and hospitalisations were combined into one outcome.	A total of 33140 infants who had received a full course of RV5 and a concurrent group of 26167 infants who had not received RV5 but had received a full course of DTaP	Vaccination codes or National drug codes o health insurance claims.	1- RR x 100 AGE outcomes were adjusted for gender and calendar year. RVGE outcomes not adjusted due to small numbers

Table S2 study characteristics of twenty three case-control studies published between January 2006 and April 2014.

Study	Country	Vaccine introduction year	Vaccine coverage	Study period	Setting	Outcome	Case definition	Control definition	Vaccine status	VE measure
Case-Control studies										
Bellido-Blasco et al. 2012	Spain (Castellon)	2006 (privately available)	21.8% (control group)	2009	Laboratory surveillance	Laboratory detection	Children 2-35 months of age with Diarrhoea and laboratory (+) RV. Mixed infections excluded	Children 2-35 months of age with AGE with laboratory (-) RV	Immunisation registry	1-OR*100 adjusted for age, hospitalisation and time of year. Logistic regression.
Braeckman et al. 2012	Belgium	2006 (National immunisation programme, partially reimbursed)	>90%	February 2008-June 2010	Random sample of 39 hospitals	Hospitalisation for RVGE	Children with AGE aged 3-59 months with laboratory (+) RV	Non-AGE controls – matched to case's DOB attending hospital or outpatient clinic.	Vaccination card or medical record	1-mOR*100 from logistic regression adjusting for sex, medical history, attendance at day care, maternal breast feeding, maternal education, attendance at preschool and household size
Carvalho-Costa et al. 2009	Brazil (Rio de Janeiro)	2006 (National immunisation programme)	58% (control group)	February 2005 to December 2007	A paediatric hospital	Hospitalisation for RVGE	Children<60 months of age with AGE and dehydration requiring IV fluid replacement with laboratory (+) RV	Children<60 months of age with AGE and dehydration requiring IV fluid replacement with laboratory (-) RV	Unknown	1-OR*100 (crude OR calculated by review team)
Castilla et al. 2012	Spain (Navarre)	2006 (privately available)	18% (control group)	January 2008- June 2011	Health service database	RVGE or AGE health care contact or Hospitalisation	Children with AGE aged 3-59 months with laboratory (+) RV	Children with AGE aged 3-59 months with laboratory (-) RV	Immunisation registry	1-OR*100, adjusting for age group, sex, birth year, major chronic conditions, health care setting and area
Correia et al. 2010	Brazil	2006 (National immunisation programme)	>50%	March 2006 - September 2008	A paediatric hospital	Hospitalisation or ED visit for RVGE	Children under 60 months of age with severe diarrhoea defined as treatment with IV fluid replacement with laboratory (+) RV	Two groups 1) Children under 60 months of age with severe diarrhoea defined as treatment with IV fluid replacement with laboratory (-) RV. 2) Children hospitalised with ARI	Vaccination card	1-OR *100 unconditional logistic regression adjusting for month and year of birth

Cortese et al. 2011	USA (Minnesota, Georgia and Connecticut)	2006	In controls 41-63% fully vaccinated	December 2006 – June 2007, December 2007- June 2008, December 2008 - June 2009	5 Hospitals	Hospitalisation or ED visit for RVGE	Children 56days and older with AGE laboratory (+) RV	Two groups: 1) Children with AGE with laboratory (-) RV. 2) Matched controls from Immunisation registry. Matched on Zip code and birth date	Hospital providers or immunisation registry	1-OR*100 adjusting for site, season and birth quarter. Exact unconditional logistic regression
Cortese et al. 2013	USA (Georgia and Connecticut)	2006	In controls 72% fully vaccinated with RV1	January 2010-June 2010 and January 2011-June 2011	5 Hospitals	Hospitalisation or ED visit for RVGE	Children >7 months of age with AGE laboratory (+) RV	Two groups: 1) Children with AGE with laboratory (-) RV. 2) Matched controls from Immunisation registry. Matched on Zip code and birth date	Hospital providers or immunisation registry	1-OR*100 adjusting for site, season and birth quarter. Exact unconditional logistic regression
Cotes-Cantillo et al. 2014	Colombia	2009 (Expanded programme of immunisation)	>90%	January 2009 - January 2011	Health centres with EDs in six cities	Hospitalisation or ED visit for RVGE	Children aged <60 months with diarrhoea and laboratory (+) RV.	Children aged <60 months with diarrhoea and laboratory (-) RV.	Vaccination card	1-OR*100 adjusting for age and birth quarter, dehydration, and vomit. Unconditional logistic regression
de Palma et al. 2010	El Salvador	2006	In controls 85%	Jan 2007 to June 2009	Seven hospitals based in cities	Hospitalisation for RVGE	Children under 60 months of age with dehydration with laboratory (+) RV	For each case three controls from the community were matched on case date of birth	Vaccination card or vaccination registry	1-OR *100 conditional logistic regression adjusting for sex, medical history, attendance at day care, maternal breast feeding and SES
Desai et al. 2010	USA (Connecticut)	2006	In controls 30%	March 2006 - July 2009	A paediatric hospital	Hospitalisation for RVGE	Children 8 weeks to 3 years of age with laboratory (+) RV	Two group 2 matched controls per group: 1) Hospitalised children with AGE (-) RV or hospitalised for non-AGE. Matched on date of birth and date of hospitalisation. 2) Non-hospitalised children registered at the same medical centre as case. Also matched for date of birth.	Medical records	1-mOR*100 from logistic regression adjusting for sex, race, ethnicity, day-care attendance, breast feeding, chronic illness, premature birth, income and tobacco exposure.

Donauer et al. 2013	USA (Rochester, Cincinnati, Nashville)	2006	74% (≥ 1 dose)	December 2006 – June 2007 and December 2007- June 2008	Prospective active population based surveillance at 3 sites	Hospitalisation or ED visit for RVGE	Lab-confirmed rotavirus in children < 3 years	Three groups: 1) Representative sub-cohort of children registered with primary care practices. 2) Children with AGE negative for RV; 3) Children with acute respiratory infection. (2&3 at same institutions as cases and matched by date of birth)	Immunisation records, immunisation registries and review of medical charts	(1) 1-HR*100 adjusted for DOB, insurance status, breast feeding and days spent at risk; (2&3) 1-OR*100, adjusted for age, breastfeeding, insurance status and site
Guh et al. 2011	USA (Connecticut)	2006	In controls 22% at least partially vaccinated	July 2006-December 2008	2 Paediatric specialty hospitals	Hospitalisation for RVGE	All infants aged ≥ 2 months but < 3 years with laboratory (+) RV	No hospitalisation for RV in study period. Matched by birth date and residence	Connecticut immunisation registry and tracking system	1-mOR*100 conditional logistic regression
Ichihara et al. 2014	Brazil	2006 (National immunisation programme)	In controls 90% at least partially vaccinated	July 2008-August 2011	National RV Acute Diarrhoea Surveillance System	Hospitalisation for RVGE	Children aged 4-24 months admitted with acute diarrhoea and (+) RV. Hospital stay at least 24 hours and first hospitalisations only.	Hospital controls recruited from same hospital as cases. No previous history RV-A diarrhoea and no vaccine preventable disease. Frequency matched for age and sex.	Vaccination card	1-OR*100, adjusting for sex and age, year of birth and robust variance estimation of Jackknife, with clusters being hospitals
Justino et al. 2011	Brazil (Belém)	2006 (National immunisation programme)	85% partially vaccinated (Community controls)	May 2008-May 2009	Active surveillance at 4 large paediatric hospitals	Hospitalisation for RVGE	Children at least 12 weeks of age hospitalised with lab-confirmed severe RVGE	Two groups: 1Community and 1 hospital control without gastroenteritis per case. Matched by birth date.	Vaccination card	1-OR*100,adjusting for potential confounders including recruitment period, underlying medical conditions, diet and breastfeeding)
Martinon-Torres et al. 2011	Spain (not reimbursed)	2008	40%	October 2008-June 2009	Paediatric research network including primary, ED and hospital settings	Any episode of RVGE and hospitalisation for RVGE	Children under 2 years seeking care due to AGE with laboratory (+) RV	Children with AGE with laboratory (-) RV	Vaccination record	1-OR*100 (crude)

Mast et al. 2011	Nicaragua	2006 (National immunisation programme)	92% partially vaccinated (Community controls)	February 2007-October 2009	Prospective active RV surveillance programme at 6 hospital sites	Hospitalisation or ED visit for RVGE	Severe (Vesikari score ≥ 11) wild type RVGE in children under 5 years	Two groups 1) Community controls, age and residence matched. 2) Hospital controls, acute non-diarrhoeal infectious disease, age-matched	Child health cards, health centre records if cards not available	1-OR*100, Final model adjusted for income, potential confounders included in univariate analysis included maternal education, gender, Maternal employment; mothers age, income, breastfeeding birth weight, premature.
Muhsen et al. 2011	Israel	2007 (partial reimbursement offered)	In controls 36% at least partially vaccinated	November 2007-December 2009	Active surveillance at 3 hospitals in Northern Israel	Hospitalisation for RVGE	Children born August 2007 or later hospitalised with laboratory (+) RV	Children hospitalised with diarrhoea with laboratory (-) RV	Parents' report	1-OR*100, adjusting for season, age, hospital, socio-economic status, birth year and month
Patel et al. 2009	Nicaragua	2006	In controls 88% were at least partially vaccinated.	2007-2008	4 hospitals in Nicaragua	RVGE requiring overnight admission (other outcome measures included but not reported here)	Children age-eligible to receive RV5 who were admitted with diarrhoea and laboratory (+) RV	Two groups: 1) Community - homes to left and right of case visited until 3 age matched controls identified 2) Hospital - children seeking care at ED or outpatient clinic, unrelated to diarrhoea or vaccine preventable illness, and matched to DOB within 30 days.	Obtained from parent and considered confirmed if vaccination card or clinic records completed.	VE = 1 –mOR x 100 Unadjusted findings presented, as adjusting for potential confounders did not change results Confounders tested included gender, underlying chronic illness, breastfeeding, day-care attendance, maternal education, no. of children, household size and socioeconomic status required to change estimate by more than 10%.

Patel et al. 2012	Nicaragua	2006	<1 Year 79% average had 1 dose over period of study. 35% average had 1 dose over period of study	2007-2010	4 community hospitals in Nicaragua	Hospitalisation with diarrhoea, laboratory (+) RV (other outcomes e.g. IV hydration – not reported here)	Children age-eligible to receive RV5 vaccine presenting with acute diarrhoea laboratory (+) RV.	Three groups: 1) Non-diarrhoea controls – matched to case's DOB from 2 sources – hospital and community. Hospital -were seeking care at ED or clinic or admitted to same hospital as the case, with an illness unrelated to diarrhoea or a vaccine preventable condition. 2) Community controls were found by visiting homes to left and right of case home until 3 controls identified. 3) Children hospitalised with diarrhoea laboratory (-) RV	Obtained from parent and considered confirmed if vaccination card or clinic records completed.	VE = 1-OR x 100 VE calculations adjusted for month of birth, age at hospitalisation, and hospital. Confounders tested included gender, underlying chronic illness, breastfeeding, day-care attendance, maternal education, no. of children, household size and socioeconomic status required to change estimate by more than 10%.
Patel et al., 2013	Bolivia	2008	National coverage 76% 2010, 80% 2011	March 2010 – June 2011	Six hospitals in Bolivia	Hospitalisation with diarrhoea, laboratory (+) RV (other outcomes considered but not presented here).	Children admitted overnight with acute diarrhoea testing positive for RV, eligible to receive at least one dose of RV1,	Two groups: 1) Hospital Controls – children admitted to same hospital for acute illness unrelated to diarrhoea or a vaccine preventable condition, eligible to receive at least 1 dose of RV1, with a DOB within 30 days of case. 2) Children hospitalised with diarrhoea lab-negative for RV	Obtained from parent and considered confirmed if vaccination card or clinic records completed.	1-adjusted OR x100 non-diarrhoea controls matched on age and hospital, and adjusted for gender, number of children and rooms at home, a computer at home. Test negative controls adjusts for age in months, month/year of birth, gender, hospital, number of children and rooms in home, computer at home.
Payne et al. 2013	USA	2006	In controls fully vaccinated with: RV1 in 2010 46%; 47% in 2011: RV5 53% in 2010 and 63% in 2011	November 2009 – June 2011	Range of surveillance hospital sites in USA.	Rotavirus disease presenting to ED or requiring hospitalisation, age-eligible for vaccination.	Children <5 years of age visiting ED or hospitalised with AGE laboratory (+) RV	Those children enrolled in the study who were found to be laboratory (-) RV	Contact with subject's primary care provider and regional immunization systems.	VE = (1-OR) x 100 Presented stratified analysis across a range of factors. Adjusted for insurance status and clinical setting but results not presented.

Snelling et al. 2011	Australia	2006	In controls 72% fully vaccinated	March – July 2011	Medical record review of all children admitted to Alice Springs hospital during an outbreak	ICD10 codes for infectious gastroenteritis in medical records. Subgroup of those RVGE positive.	All children aged <5 admitted to Alice Springs Hospital with gastroenteritis during an outbreak, with ICD10 codes for infectious gastroenteritis	Retrospectively conducted matched controls from a record of central Australian births registered on hospital information database.	Vaccination determined from central immunisation database.	VE = 1-OR x 100 (Cases and controls matched for indigenous status and date of birth (within 7 days). Adjusted for remote residence.
Staat et al. 2011	USA	2006	In controls 54% any dose	2007-2009 rotavirus seasons	Prospective surveillance conducted in 3 US counties as part of New Vaccine Surveillance Network	Hospitalisations and ED visits for RVGE in children attending the surveillance hospitals during the rotavirus seasons.	All children attending the ED or hospitalised with AGE with laboratory (+) RV	Two groups: 1) Children with AGE with laboratory (-) RV. 2) ARI controls: children with ARI symptoms who were residents of same study county.	Parents documentation of vaccination. If not available, obtained from state registries.	VE = (1-OR) x 100 Cases were matched to controls according to DOB and symptom onset date. Adjusted for insurance status and clinical setting.

VE= vaccine effectiveness; RVGE=rotavirus gastroenteritis; AGE=acute gastroenteritis; RR= relative risks / risk ratios; IRR=incidence rate ratio; ARI= acute respiratory infection; ED= emergency department; (+) RV = laboratory confirmed positive rotavirus; (-) RV = laboratory confirmed negative rotavirus; mOR = matched Odds Ratio; DTaP = diphtheria, tetanus, acellular polio; RV1= Rotarix vaccine; RV5= RotaTeq vaccine; HR= Hazard rate ratio

Table S3 Yearly rates of hospitalisation/attendance for different levels of the health system pre- and post-rotavirus vaccine introduction in Merseyside, UK.

Age group	Yearly rate of hospitalisation / attendance (per 10,000)[¥]															
	Pre-vaccine Introduction													Post-vaccine introduction		
	2000/01	2001/02	2002/03	2003/04	2004/05	2005/06	2006/07	2007/08	2008/09	2009/10	2010/11	2011/12	2012/13	2013/14	2014/15	2015/16
Hospitalisations for laboratory confirmed rotavirus to Alder Hey																
<12m	-	-	158	168	148	182	85	123	85	113	125	130	168	16	23	4
12-23m	-	-	159	118	145	157	88	140	97	130	136	112	102	30	19	0
24-59m	-	-	44	36	30	48	28	42	25	33	23	26	40	5	17	7
5-14y	-	-	7	6	5	8	6	9	8	9	11	6	6	1	1	0
Total 0-59m	-	-	106	98	93	121	62	94	63	84	84	82	96	14	19	5
Hospitalisations for all cause acute gastroenteritis																
<12m	351	322	312	353	285	387	563	577	492	580	363	298	328	249	222	220
12-23m	251	227	233	231	209	259	335	343	295	404	244	227	254	138	124	123
24-59m	68	63	68	55	58	63	98	94	91	98	63	51	63	42	67	53
5-14y	14	13	12	13	13	17	25	25	25	28	22	16	20	18	19	22
15-64y	30	27	27	25	29	32	44	49	45	46	48	53	55	56	61	63
65+	82	87	111	101	117	120	169	173	158	155	140	160	172	151	159	159

Age group	Yearly rate of hospitalisation / attendance (per 10,000)¥															
	Pre-vaccine Introduction													Post-vaccine introduction		
	2000/01	2001/02	2002/03	2003/04	2004/05	2005/06	2006/07	2007/08	2008/09	2009/10	2010/11	2011/12	2012/13	2013/14	2014/15	2015/16
Total 0-59m	156	143	147	148	135	169	243	247	217	260	161	137	158	103	109	100
ED attendances for gastrointestinal conditions (no admission)																
<12m	-	-	-	-	-	-	-	-	1654	1889	2101	2280	2240	1959	2115	1610
12-23m	-	-	-	-	-	-	-	-	978	1003	1102	1314	1340	942	1050	758
24-59m	-	-	-	-	-	-	-	-	650	691	750	828	887	800	945	604
5-14y	-	-	-	-	-	-	-	-	406	456	584	656	711	698	712	601
15-64y	-	-	-	-	-	-	-	-	286	304	375	525	630	606	507	432
65+	-	-	-	-	-	-	-	-	237	278	350	404	521	545	443	366
Total 0-59m	-	-	-	-	-	-	-	-	1022	1105	1239	1395	1425	1180	1332	948
Walk-in centre attendances for infectious gastroenteritis*																
<12m	-	-	-	-	-	-	-	-	-	-	-	604	580	369	378	371
12-23m	-	-	-	-	-	-	-	-	-	-	-	468	488	249	325	206
24-59m	-	-	-	-	-	-	-	-	-	-	-	209	184	144	176	143
5-14y	-	-	-	-	-	-	-	-	-	-	-	81	78	66	89	60
15-64y	-	-	-	-	-	-	-	-	-	-	-	56	56	45	52	54
65+	-	-	-	-	-	-	-	-	-	-	-	15	29	16	20	19
Total 0-59m	-	-	-	-	-	-	-	-	-	-	-	380	361	223	262	211

Age group	Yearly rate of hospitalisation / attendance (per 10,000)¥															
	Pre-vaccine Introduction													Post-vaccine introduction		
	2000/01	2001/02	2002/03	2003/04	2004/05	2005/06	2006/07	2007/08	2008/09	2009/10	2010/11	2011/12	2012/13	2013/14	2014/15	2015/16
GP consultations for infectious gastroenteritis																
<12m	-	-	-	-	-	-	_	712	678	677	697	625	658	452	524	500
12-23m	-	-	-	-	-	-	_	692	567	652	500	558	582	335	488	429
24-59m	-	-	-	-	-	-	_	183	187	209	178	164	182	125	209	164
5-14y	-	-	-	-	-	-	_	56	49	55	56	50	52	46	62	60
15-64y	-	-	-	-	-	-	_	43	37	41	41	40	41	28	36	26
65+	-	-	-	-	-	-	_	30	30	35	34	36	44	28	33	26
Total 0-59m	-	-	-	-	-	-	_	391	361	391	346	335	357	232	328	284